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# Clinical, Radiological, and Molecular Profiles of Rifampicin-resistant Pulmonary Tuberculosis: A Cross-sectional Study from a Tertiary Referral Center in Indonesia

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## Abstract

**Rifampicin-resistant tuberculosis (RR-TB) remains a major public health concern, and is characterized by diagnostic challenges and suboptimal treatment success. To better understand the factors influencing disease burden and outcomes, the present study investigated the clinical, demographic, radiological, and molecular characteristics of patients in a high-burden tertiary hospital in Indonesia. A cross-sectional study involving adult patients diagnosed with RR-TB at Dr. Soetomo General Hospital (Surabaya, Indonesia) was conducted to analyze clinical symptoms, comorbidities, radiographic findings, treatment regimens, and laboratory data, including sputum smear grades and IS6110–IS1081 cycle threshold (CT) values. Among 55 patients with RR-TB (mean age 45.1 years; 60% male), IS6110–IS1081 CT values exhibited significant inverse associations with the Modified Bandim TB Score (p = 0.002) and chest pain (p = 0.003), indicating higher bacterial burden in more symptomatic patients. CT values were also negatively correlated with sputum smear scores (r = -0.342; p = 0.011). Treatment failure was independently associated with anemia (odds ratio [OR] 13.2, p = 0.023) and a long-course regimen (OR 7.3, p = 0.026). A higher bacterial burden, as reflected by lower IS6110–IS1081 CT values, was associated with greater disease severity and chest pain. Anemia and long-course regimens independently predicted treatment failure, highlighting the need for the early detection of patients at high risk and optimized treatment strategies for RR-TB management.**

**Keywords:** Rifampicin-resistant Tuberculosis, Cycle Threshold Value, Sputum Smear, Molecular Diagnostics

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## INTRODUCTION

Rifampicin-resistant tuberculosis (RR-TB) is a critical global health challenge due to its diagnostic complexity and poor treatment outcomes. *Mycobacterium tuberculosis* (MTB), the causative agent of TB, primarily spreads through the inhalation of infected aerosols. In the lungs, MTB is phagocytosed by alveolar macrophages and forms granulomas, which can reactivate under immunocompromised conditions.[1,2] One-quarter of the global population is infected, with 6.9 million pulmonary TB cases reported in 2023, of which 5.5% exhibited drug resistance, including 159,684 RR-TB and 28,982 pre-extensively drug-resistant (pre-XDR)/XDR cases.[2]

Drug-resistant TB leads to severe clinical manifestations and high mortality, particularly among vulnerable groups.[3,4] In 2021, RR-TB accounted for approximately 191,000 deaths (World Health Organization [WHO], 2022). Indonesia remains among the countries with the highest RR-TB burden, where treatment was initiated in only 62% of confirmed cases in 2022, and treatment success was merely 51%.[5] Rifampicin resistance, driven mainly by *rpoB* gene mutations altering the RNA polymerase β-subunit,[6] results in longer, more toxic, and less effective therapy.[7]

Although culture remains the gold-standard diagnostic method, its complexity limits its use in low-resource settings.[8] Sputum smear microscopy, while rapid, has limited sensitivity (78.6%) and requires skilled technicians.[9,10] The GeneXpert Ultra assay (Cepheid, Sunnyvale, CA, USA) offers higher sensitivity (131-250 colony-forming units/mL) and simultaneously detects MTB and rifampicin resistance.[11,12] It also provides cycle threshold (CT) values reflecting the bacterial DNA load, with lower CT values indicating higher bacillary burden.[13,14]

Higher sputum smear scores have been associated with greater disease severity[15]; however, their correlation with the clinical and molecular features of RR-TB remains underexplored, particularly in Indonesia. As such, the present study investigated the relationship between sputum smear score, IS6110–IS1081 CT values, and clinical findings among patients diagnosed with RR-TB at Dr. Soetomo Hospital, (Surabaya, Indonesia) to support improved diagnostic interpretation and treatment outcomes.

## MATERIALS AND METHODS

This prospective observational study, with a descriptive–analytic design, investigated the associations between sputum smear scores, IS6110–IS1081 CT values, and the clinical characteristics of patients diagnosed with RR-TB. This study was conducted at the Dr. Soetomo General Hospital, Surabaya, Indonesia, using data collected between January 2023 and April 2025. Ethics approval was obtained from the Health Research Ethics Committee of the Dr. Soetomo General Hospital (Ethical Clearance No. 1980/LOE/301.4.2/V/2025). Because this study used anonymized secondary data from medical records, requirements for individual informed consent were waived. The Ethics Committee approved the use of patient records and waived the requirement for written consent because no direct patient contact or intervention occurred. Data extraction from medical records was performed once outside the patients' treatment period in accordance with institutional data protection policies.

The study population included all adult (≥18 years of age) patients diagnosed with RR-TB who were treated during the study period. Patients were enrolled consecutively if they had a confirmed diagnosis of RR-TB according to the GeneXpert MTB/RIF Ultra assay and complete medical records, including sputum smear results, IS6110 and IS1081 CT values, and relevant clinical and radiological data. Patients with incomplete data and those who died before treatment initiation were excluded.

All CT values were obtained using the GeneXpert MTB/RIF Ultra platform operated under standardized laboratory procedures and environmental conditions. For each patient, individual CT values for the IS6110 and IS1081 targets were recorded separately, as reported by the system. These values were subsequently tabulated and analyzed to evaluate their associations with clinical, bacteriological, and radiological parameters, with no averaging or transformation performed before analysis. Clinical data, including demographic characteristics, clinical symptoms, laboratory results, radiological

findings, and treatment regimens and outcomes, were collected prospectively. The primary variables of interest were sputum smear scores and IS6110–IS1081 CT values, which were used as indicators of bacterial burden. The independent variables included demographic, clinical, and radiological profiles, as well as treatment-related factors.

The Modified Bandim TB Score was used to assess disease severity. The original Bandim TB Score comprised 13 items (each scored 1 point; maximum 13 points) covering cough, hemoptysis, dyspnea, chest pain, night sweats, anemic conjunctiva, tachycardia, positive auscultation findings, axillary temperature > 37 °C, body mass index (BMI) BMI <18 kg/m$^2$, BMI <16 kg/m$^2$, mid-upper arm circumference (MUAC) <220 mm, and MUAC <200 mm. In this study, MUAC was not measured; therefore, the maximum possible score was 11. The total scores were categorized as follows: 0-5, severity classification (SC) I (mild); 6-7, SC II (moderate); and 8-11, SC III (severe). For analytical purposes, scores of 6-11 were classified as "moderate-to-severe".

All statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Data normality was assessed using the Kolmogorov–Smirnov test. Non-parametric tests, including chi-squared, Kruskal–Wallis, Mann–Whitney U, and Spearman's correlation, were used for bivariate analysis. Multivariate analysis was performed using linear regression for the predictors of CT values and logistic regression for the determinants of treatment failure. Differences with $p < 0.05$ were considered to be statistically significant. Given the modest sample size, no formal power analysis was performed, which may be considered a limitation of the study. Multivariate models were interpreted cautiously to minimize overfitting and to account for potential confounders, including disease severity (Modified Bandim TB Score) and radiological features such as cavity formation.

## RESULTS

Data from 55 patients who were diagnosed with RR-TB and fulfilled the inclusion criteria were included in this study. The mean patient age was 45.1 years, with the largest proportion falling within the 46-65-years' age group (54.5%), and the majority were male (60%). The mean height and weight were 159.1 cm and 51.5 kg, respectively, with a mean BMI of 20.5 kg/m$^2$; more than one-half of patients (56.4%) had a normal BMI. Most patients (74.5%) had newly diagnosed TB. Diabetes mellitus was the most prevalent comorbidity (52.7%), followed by HIV (9.1%). The most commonly administered treatment regimens were BPALM (bedaquiline, pretomanid, linezolid, and moxifloxacin [47.3%]) and short-course (61.8%) regimens. Treatment outcomes were distributed as follows: cure (30.9%); death (16.4%); and loss to follow-up (10.9%) (Table 1).

Statistical testing using the Kolmogorov–Smirnov method indicated that most data were not normally distributed; however, data homogeneity enabled the use of non-parametric tests for further analysis. Evaluation of the association between sputum smear scores and clinical characteristics revealed no significant correlations. Age, sex, BMI, TB treatment history, and the presence of comorbidities, such as diabetes mellitus and HIV, did not differ significantly across the smear score categories. Although chest pain appeared more frequently in the higher smear score group, the association was not statistically significant ($p = 0.059$). The Modified Bandim TB Score tended to increase with higher smear scores, although the difference was not statistically significant ($p = 0.171$). Similarly, radiological features, such as cavities, fibrosis, nodules, and pleural effusion, were distributed across the smear score groups without significant variation. No clinical or demographic variables demonstrated a statistically significant association with sputum smear score, although some trends may have clinical implications (Table S1).

Analysis of IS6110–IS1081 CT values also demonstrated no significant association with most patient characteristics, including age, sex, BMI, treatment history, or treatment outcome. Common clinical symptoms, such as fever, cough, dyspnea, night sweats, anemia, and abnormal auscultation findings, were not significantly correlated with CT values. Radiological findings revealed no significant associations. However, two noteworthy findings emerged. First, a significant association was found between CT values and the Modified Bandim TB Score ($p = 0.027$): patients

**Table 1.** Characteristics of Patients with Rifampicin-Resistant Pulmonary TB (n = 55)

| Variable | Value |
|---|---|
| **Age, years (Mean ± SD)** | 45.1 ± 13.2 |
| Age categories, n (%) | |
| 18-25 years | 6 (10.9%) |
| 26-45 years | 17 (30.9%) |
| 46-65 years | 30 (54.5%) |
| >65 years | 2 (3.6%) |
| Sex, n (%) | |
| Male | 33 (60%) |
| Female | 22 (40%) |
| **Height, cm (Mean ± SD)** | 159.1 ± 10.9 |
| **Weight, kg (Mean ± SD)** | 51.5 ± 11.2 |
| **BMI, kg/m² (Mean ± SD)** | 20.5 ± 5.0 |
| BMI categories, n (%) | |
| >25(Overweight) | 7 (12.7%) |
| 18.5-24.9 (Normal) | 31 (56.4%) |
| 16-18.4 (Mild–Moderate Underweight) | 8 (14.5%) |
| <16 (Severe Underweight) | 9 (16.4%) |
| History of TB treatment, n (%) | |
| New case | 41 (74.5%) |
| Relapse | 8 (14.5%) |
| Lost to follow-up (LTFU) | 6 (10.9%) |
| Comorbidities, n (%) | |
| Diabetes Mellitus (DM) | 29 (52.7%) |
| HIV | 5 (9.1%) |
| Anti-TB treatment regimen duration, n (%) | |
| Short-term regimen | 34 (61.8%) |
| Long-term regimen | 21 (38.2%) |
| Initial treatment regimens, n (%) | |
| 6 Bdq-Lfx-Lzd-Cfz-Cs-VitB6/14 Lfx-Cfz-Cs-VitB6 | 1 (1.8%) |
| 6 Lfx-Lzd-Cfz-Cs-Amk-VitB6/14 Lfx-Lzd-Clz-Cs-VitB6 | 20 (36.4%) |
| 6 Bdq-Lfx-Eto-E-Z-Hh-Cfz/5 Lfx-Cfz-Z-E (Non-injectable STR) | 6 (10.9%) |
| BPAL (Bedaquiline-Pretomanid-Linezolid) | 2 (3.6%) |
| BPALM (Bedaquiline-Pretomanid-Linezolid-Moxifloxacin) | 26 (47.3%) |
| Treatment outcomes, n (%) | |
| Failure due to diagnosis change | 5 (9.1%) |
| Lost to follow-up (LTFU) | 6 (10.9%) |
| Death | 9 (16.4%) |
| Still on treatment | 18 (32.7%) |
| Cured | 17 (30.9%) |
| **CT Value IS6110–IS1081 (Mean ± SD)** | 18.8 ± 4 |
| Baseline Sputum Smear (AFB), n (%) | |
| 0 | 24 (43.6%) |
| Scanty | 3 (5.5%) |
| +1 | 14 (25.5%) |
| +2 | 5 (9.1%) |
| +3 | 9 (16.4%) |
| **Modified Bandim TB Score (Mean ± SD)** | 5.5 ± 2.7 |
| Modified Bandim TB Score category, n (%) | |
| Mild | 30 (54.5%) |
| Moderate–Severe | 25 (45.5%) |
| Clinical manifestations, n (%) | |
| Body temperature >37 °C | 37 (67.3%) |
| Cough | 54 (98.2%) |
| Hemoptysis (coughing blood) | 16 (29.1%) |
| Shortness of breath | 37 (67.3%) |
| Night sweats | 31 (56.4%) |
| Chest pain | 19 (34.5%) |
| Heart rate >90 bpm | 36 (65.5%) |
| Anemia (Hb <13 g/dL male / <12 g/dL female) | 19 (34.5%) |
| Positive auscultation (rhonchi/ crepitations) | 29 (52.7%) |
| Radiological findings, n (%) | |
| Atelectasis | 2 (3.6%) |
| Pleural effusion | 2 (3.6%) |
| Fibrosis | 7 (12.7%) |
| Fibrothorax | 2 (3.6%) |
| Cavities | 19 (34.5%) |
| Consolidation | 1 (1.8%) |
| Miliary | 1 (1.8%) |
| Nodules | 21 (38.2%) |

BMI: Body Mass Index; TB: Tuberculosis; LTFU: Lost to Follow-Up; DM: Diabetes Mellitus; Bdq: Bedaquiline; Lfx: Levofloxacin; Lzd: Linezolid; Cfz: Clofazimine; Cs: Cycloserine; Am: Amikacin; Eto: Ethionamide; E: Ethambutol; Z: Pyrazinamide; Hh: High-Dose Isoniazid; STR: Streptomycin; SD: Standard Deviation; Hb: Hemoglobin; AFB: Acid-Fast Bacilli

with mild disease exhibited higher mean CT values (20.2 ± 4.8), reflecting a lower bacterial burden, compared to those with moderate-to-severe scores (17.0 ± 1.8) (Table 2). This relationship was confirmed by multivariate linear regression (p = 0.002), yielding the following model: CT value = 23.535 – 3.271 × Bandim Score. Second, chest pain was significantly associated with lower CT values (p = 0.015), suggesting a higher bacterial load: multivariate analysis supported this finding (p = 0.003), with the regression equation: CT value = 19.936 – 3.357 × chest pain.

A statistically significant inverse relationship was found between sputum smear scores and IS6110–IS1081 CT values (Table 3).

**Table 2.** Association between IS6110-IS1081 CT Value and Characteristics of Patients with Rifampicin-Resistant Pulmonary TB

| Variable | CT Value (Mean ± SD) | p-value |
|---|---|---|
| Age | | 0.143[1] |
| 18-25 years (n = 6) | 19.9 ± 5.4 | |
| 26-45 years (n = 17) | 18.1 ± 3.5 | |
| 46-65 years (n = 30) | 19.1 ± 4.2 | |
| >65 years (n = 2) | 16.1 ± 0.0 | |
| Sex | | 0.959[2] |
| Male (n = 33) | 19.2 ± 4.4 | |
| Female (n = 22) | 18.1 ± 3.4 | |
| BMI (kg/m²) | | 0.081[1] |
| >25 (n = 7) | 19.4 ± 4.8 | |
| 18.5–24.9 (n = 31) | 19.5 ± 4.3 | |
| 16–18.4 (n = 8) | 17.9 ± 4.1 | |
| <16 (n = 9) | 16.5 ± 1 | |
| Treatment History | | 0.820[1] |
| New (n = 41) | 18.9 ± 4 | |
| Relapse (n = 8) | 18.7 ± 4.3 | |
| LTFU (n = 6) | 18.2 ± 4.6 | |
| Treatment Outcome | | 0.821[1] |
| Failure due to diagnosis change (n = 5) | 21 ± 6.5 | |
| LTFU (n = 6) | 17.3 ± 1.9 | |
| Death (n = 9) | 17.6 ± 2.7 | |
| Under treatment (n = 18) | 18.4 ± 3.7 | |
| Cured (n = 17) | 19.7 ± 4.6 | |
| Modified Bandim TB Score (Mean ± SD) | 18.8 ± 4 | |
| Modified Bandim TB Score | | 0.027[2] |
| Mild (n = 30) | 20.2 ± 4.8 | |
| Moderate-Severe (n = 25) | 17 ± 1.8 | |
| Clinical Manifestations | | |
| Temperature >37 °C (n = 37) | 18.3 ± 3.7 | 0.260[2] |
| Cough (n = 54) | 18.6 ± 4 | 0.218[2] |
| Hemoptysis (n = 16) | 18.2 ± 4.2 | 0.183[2] |
| Dyspnea (n = 37) | 18.2 ± 3.4 | 0.564[2] |
| Night sweats (n = 31) | 17.8 ± 3.1 | 0.078[2] |
| Chest pain (n = 19) | 16.6 ± 0.8 | 0.015[2] |
| HR >90 bpm (n = 36) | 18.1 ± 3.4 | 0.540[2] |
| Anemia (n = 19) | 17.1 ± 1.4 | 0.429[2] |
| Positive auscultation (n = 29) | 18.3 ± 3.7 | 0.379[2] |
| Radiologic Manifestations | | |
| Atelectasis (n = 2) | 16.2 ± 0.1 | 0.264[2] |
| Pleural effusion (n = 2) | 20.6 ± 6.1 | 0.512[2] |
| Fibrosis (n = 7) | 19.1 ± 4.4 | 0.739[2] |
| Fibrothorax (n = 2) | 16.2 ± 0.2 | 0.436[2] |
| Cavities (n = 19) | 18.6 ± 4.2 | 0.908[2] |
| Consolidation (n = 1) | 16 ± – | 0.109[2] |
| Miliary pattern (n = 1) | 16.6 ± – | 0.945[2] |
| Nodules (n = 21) | 19.3 ± 4.2 | 0.424[2] |

Note: [1]Kruskal-Wallis test (for variables with >2 categories)
[2]Mann-Whitney test (for binary variables)

**Table 3.** Association Between Sputum Smear Score and IS6110-IS1081 CT Value in Patients with Rifampicin-Resistant Pulmonary TB

| Variable | IS6110-IS1081 CT Value (Mean ± SD) | r (Spearman Correlation) | p-value |
|---|---|---|---|
| Sputum Smear Score | | | |
| 0 | 20.5 ± 4.7 | | |
| Scanty | 20.3 ± 3.2 | | |
| +1 | 17.8 ± 3.8 | | |
| +2 | 16.7 ± 0.8 | | |
| +3 | 16.4 ± 0.7 | | |
| Total (All Groups) | 18.8 ± 4 | r = -0.342 | 0.011 |

The mean CT values declined progressively, from 20.5 in smear-negative patients to 16.4 in those with a smear score of +3. This modest, but significant, negative correlation (r = -0.342; p = 0.011) indicated that higher smear grades were associated with lower CT values, reflecting a greater bacterial burden. Multivariate linear regression confirmed this association (p = 0.036) using the equation: CT value = 2.851 – 0.091 × sputum smear score. Although the coefficient of determination was low ($R^2$ = 0.080), the results suggest that the smear score may independently predict bacterial load.

Finally, analysis of factors associated with treatment failure revealed significant associations with treatment regimen (p = 0.039), anemia (p = 0.005), and specific radiological findings, particularly cavitation (p = 0.028) and fibrothorax (p = 0.024). Patients who underwent long-course regimens experienced higher treatment failure rates than those who underwent short-course regimens. Anemia was markedly more prevalent among patients who experienced treatment failure (Table 4). Multivariate logistic regression analysis identified anemia (odds ratio [OR] 13.211; p = 0.023) and a long-course regimen (OR 7.302; p = 0.026) as independent predictors of treatment failure. Although cavity formation exhibited a trend toward increased risk (OR 4.254), it did not reach statistical significance (p = 0.113), and fibrothorax was excluded from the model due to undefined odds (Table 5).

**Table 4.** Factors Associated with Treatment Failure

| Variable | Treatment Failure N = 38 | Treatment Success N = 17 | p-value |
|---|---|---|---|
| **Age, years, n (%)** | | | 0.681[1] |
| 18-25 years (n = 6) | 5 (13.2%) | 1 (5.8%) | |
| 26-45 years (n = 17) | 12 (31.6%) | 5 (29.4%) | |
| 46-65 years (n = 30) | 19 (50%) | 11 (64.7%) | |
| >65 years (n = 2) | 2 (5.2%) | 0 (0%) | |
| **Sex, n (%)** | | | 0.808[2] |
| Male (n = 33) | 22 (57.9%) | 11 (64.7%) | |
| Female (n = 22) | 16 (42.1%) | 6 (35.3%) | |
| **BMI (kg/m²), n (%)** | | | 0.269[1] |
| ≥25 (n = 7) | 6 (15.8%) | 1 (5.9%) | |
| 18.5-24.9 (n = 31) | 21 (55.3%) | 10 (58.8%) | |
| 16-18.4 (n = 8) | 4 (10.5%) | 4 (23.5%) | |
| <16 (n = 9) | 7 (18.4%) | 2 (11.7%) | |
| **Treatment History, n (%)** | | | 0.809[1] |
| New (n = 41) | 28 (73.6%) | 13 (76.5%) | |
| Relapse (n = 8) | 6 (15.8%) | 2 (11.7%) | |
| LTFU (n = 6) | 4 (10.5%) | 2 (11.7%) | |
| Comorbidities, n (%) | | | |
| Diabetes Mellitus (n = 29) | 21 (55.3%) | 8 (47%) | 0.795[2] |
| HIV (n = 5) | 3 (7.9%) | 2 (11.8%) | 0.573[2] |
| Anti-TB Treatment Regimen Duration, n (%) | | | 0.039[2] |
| Short-term (n = 34) | 20 (52.6%) | 14 (82.3%) | |
| Long-term (n = 21) | 18 (47.4%) | 3 (17.6%) | |
| **CT Value IS6110–IS1081 (Mean ± SD)** | 18.3 ± 3.7 | 19.9 ± 4.6 | 0.372[3] |
| **Baseline Sputum Smear, n (%)** | | | 0.758[1] |
| 0 | 18 (47.4%) | 6 (35.3%) | |
| Scanty | 2 (5.3 | | |
| +1 | 7 (18.4%) | 7 (37.5%) | |
| +2 | 4 (10.5%) | 1 (5.9%) | |
| +3 | 7 (18.4%) | 2 (11.8%) | |
| **Modified Bandim TB Score (Mean ± SD)** | 5.7 ± 2.7 | 4.8 ± 2.7 | |
| **Modified Bandim TB Score** | | | 0.175[2] |
| Mild (n = 30) | 18 (47.4%) | 12 (70.6%) | |
| Moderate–Severe (n = 25) | 20 (52.6%) | 5 (29.4%) | |
| Clinical Manifestations | | | |
| Temperature >37°C (n = 37) | 29 (76.3%) | 8 (47%) | 0.080[2] |
| Cough (n = 54) | 38 (100%) | 16 (94.1%) | 0.115[2] |
| Hemoptysis (n = 16) | 12 (30.8%) | 4 (23.5%) | 0.669[2] |
| Dyspnea (n = 37) | 26 (66.7%) | 11 (64.7%) | 0.881[2] |
| Night sweats (n = 31) | 23 (59%) | 8 (47%) | 0.542[2] |
| Chest pain (n = 19) | 14 (35.9%) | 5 (29.4%) | 0.742[2] |
| HR >90 bpm (n = 36) | 26 (66.7%) | 10 (58.8%) | 0.768[2] |
| Anemia (n = 19) | 18 (46.2%) | 1 (5.9%) | **0.005[2]** |
| Positive auscultation (n = 29) | 19 (48.7%) | 10 (58.8%) | 0.352[2] |

**Table 4.** Cont...

| Variable | Treatment Failure N = 38 | Treatment Success N=17 | p-value |
|---|---|---|---|
| Radiologic Manifestations | | | |
| Atelectasis (n = 2) | 1 (2.6%) | 1 (5.9%) | 0.507[2] |
| Pleural effusion (n = 2) | 1 (2.6%) | 1 (5.9%) | 0.507[2] |
| Fibrosis (n = 7) | 3 (7.7%) | 4 (23.5%) | 0.080[2] |
| Fibrothorax (n = 2) | 0 (0%) | 2 (11.8%) | **0.024**[2] |
| Cavities (n = 19) | 17 (43.6%) | 2 (11.8%) | **0.028**[2] |
| Consolidation (n = 1) | 1 (2.6%) | 0 (0%) | 0.518[2] |
| Miliary pattern (n = 1) | 1 (2.6%) | 0 (0%) | 0.518[2] |
| Nodules (n = 21) | 15 (38.5%) | 6 (35.3%) | 0.947[2] |

**Notes**: [1]Kruskal-Wallis Test for variables with ≥3 categories; [2]Chi-square Test for variables with 2 categories; [3]Mann-Whitney Test for continuous variables; * p < 0.05 indicates statistical significance

**Table 5.** Multivariate Logistic Regression Analysis of Factors Associated with Treatment Failure

| Factor | p-value | OR | 95% CI |
|---|---|---|---|
| Long-course treatment regimen | 0.026* | 7.302 | (1.265-42.144) |
| Anemia | 0.023* | 13.211 | (1.431-121.925) |
| Fibrothorax | 0.999 | 0.000 | (0.000 - –) |
| Cavity | 0.113 | 4.254 | (0.709-25.523) |

* p < 0.05 indicates statistical significance

## DISCUSSION

Indonesia, one of the countries with the highest TB burden in Southeast Asia, faces substantial challenges in terms of TB control and management. Along with Bangladesh and the Philippines, Indonesia accounted for 18% of global TB incidence in 2017, recording an estimated 969,000 new or relapsed TB cases in 2021.[16,17] Indonesia faces a substantial detection and notification gap—55% of estimated TB cases in 2021 were undiagnosed or unreported, higher than India (33%) and Bangladesh (18%) but lower than Myanmar (67%).[17] Only 30% of infectious TB cases were detected, similar to the Philippines (22%) and far below Bangladesh's near-total detection.[16] Drug-resistant TB poses a major obstacle: the Southeast Asia (SEA) region accounted for 38% of the global multidrug-resistant (MDR)/RR-TB burden in 2021, and Indonesia is classified among the high-burden countries for MDR/RR-TB, struggling with one of the highest notification gaps regionally (70%).[17] The Philippines, classified within the SEA/WPR region, was estimated to have 9000 MDR-TB cases in 2019, while Vietnam had 6000. Moreover, research has projected that the proportion of MDR-TB cases in the Philippines will increase to 8.9% by 2040.[18] In terms of workplace TB policies, the Philippines leads the region with the most comprehensive coverage (13 of 17 WHO/International Labour Organization-recommended components), ahead of Myanmar, Malaysia, and Cambodia.[19] Overall, Indonesia shares key challenges with the Philippines—high infectious TB prevalence and wide notification gaps—while also contending with one of the highest MDR-TB burdens in the region.[17]

The present study provides a comprehensive overview of the demographic, clinical, radiological, and molecular characteristics of patients with RR-TB treated at the Dr. Soetomo General Hospital, Surabaya. Most patients were male and within the productive age range (20-50 years), aligning with global epidemiological trends that associate this group with a higher TB risk due to increased social mobility, occupational exposure, and broader interaction networks.[20-22] The observed male predominance is consistent with previous findings and may be attributed to behavioral factors, such as smoking and treatment adherence,[20,23] although disparities in access to

healthcare may place women at increased risk in specific settings.[24]

While most patients had a normal BMI, cases of malnutrition (BMI <18.5 kg/m$^2$) and anemia were notable. Both conditions are established risk factors for TB, and are associated with impaired immunity and poor outcomes. Anemia alone may increase TB susceptibility up to four-fold.[25] Nutritional interventions—including individualized dietary plans, micronutrient supplementation, and ongoing counseling—have demonstrated efficacy in improving treatment outcomes.

Interestingly, the majority of cases were newly diagnosed, even though previous TB treatment history remains a strong predictor of RR-TB, with an estimated five-fold increased risk.[23] This trend suggests that the transmission of resistant MTB strains is increasingly driven by community spread rather than acquired resistance, potentially facilitated by compensatory mutations that enhance bacterial fitness.[26-28] These findings emphasize the need for early drug-resistance screening, even in treatment-naıve patients.

Diabetes mellitus emerged as the most common comorbidity, consistent with its known role in increasing both TB-specific and all-cause mortality (OR 1.90 and 4.54, respectively), largely due to impaired immune responses and reduced therapeutic efficacy.[29] Although HIV co-infection was rare in this cohort, it remains clinically significant given its association with a more than 28-fold increase in TB mortality and substantial treatment complexity.

Most patients were managed using the WHO-recommended, short-course BPaLM regimen (bedaquiline, pretomanid, linezolid, and moxifloxacin), which has demonstrated high effectiveness and favorable adherence profiles in other high-burden settings.[30,31] The average treatment duration was 26 weeks, which was extended to 39 weeks based on clinical or radiological response(s). Adverse effects, primarily anemia, neuropathy, and gastrointestinal symptoms, were generally mild to moderate and managed without treatment discontinuation, underscoring the importance of structured pharmacovigilance to ensure adherence.

Laboratory data revealed that many smear-negative patients had low IS6110–IS1081 CT values, indicating a substantial bacillary load detectable only via molecular methods. This highlights the limitations of smear microscopy—particularly in RR-TB—and supports the superior sensitivity of digital polymerase chain reaction (dPCR) as demonstrated by Li et al.[14] Clinical symptoms, such as cough, fever, and dyspnea, are common, whereas radiological findings are dominated by cavitary and nodular lesions, fibrosis, and pleural effusion, which are the hallmarks of advanced pulmonary damage.

Although no significant associations were observed between sputum smear scores and clinical, demographic, or radiological features, a modest but consistent inverse correlation was found between smear scores and CT values ($r = -0.342$; $p = 0.011$). This finding supports the biological plausibility that a higher bacillary load corresponds to lower CT values because lower CTs indicate higher concentrations of MTB DNA. Smear-negative and scanty cases demonstrated the highest mean CT values (20.5 ± 4.7 and 20.3 ± 3.2), whereas patients with +2 and +3 smear scores exhibited notably lower mean CT values (16.7 ± 0.8 and 16.4 ± 0.7). This trend aligns with the quantitative principle of PCR, in which amplification occurs more rapidly in samples with higher DNA content.[32] Similarly, Gota, Shenoy, and Kamath[14] reported a stronger polychoric correlation ($\rho = -0.8681$) between smear grade and CT, reinforcing the robustness of this inverse relationship. Although Li et al.[33] did not directly analyze smear correlation, their work supports the high sensitivity of dPCR for detecting MTB DNA, even in smear-negative specimens.[33]

CT values were further associated with clinical severity: lower values were significantly associated with higher Modified Bandim TB scores and the presence of chest pain. Multivariate analysis confirmed that both variables were independently correlated with CT values ($p = 0.036$; $\beta = -0.091$) despite the limited explanatory power of the model ($R^2 = 0.080$). This suggests that smear scores and CT values, while related, are influenced by distinct factors, such as bacterial viability, DNA degradation, and host immune

status. CT overlaps across smear categories and instances of low CT values in culture-negative samples,[14] further indicating that PCR may detect nonviable DNA, thereby limiting its utility in assessing infectivity.

Importantly, treatment failure was independently associated with prolonged therapy and the presence of anemia, both of which exhibited statistically significant ORs. These results underscore the multifactorial nature of RR-TB treatment outcomes and the need for integrated clinical decision making that considers biological, treatment-related, and host-specific variables.

## CONCLUSION

Results of the present study reinforce that, while smear microscopy retains value for assessing infectivity, it is limited in sensitivity and is poorly correlated with clinical and radiological severity. In contrast, molecular diagnostics, particularly CT values from PCR assays, offer a more precise and quantitative estimation of bacillary burden and may better reflect clinical severity. However, CT values alone are insufficient for predicting treatment outcomes due to technical and biological variability. Thus, an integrated approach that combines molecular diagnostics with clinical scoring systems, radiological assessments, and patient profiling is essential for effective management of RR-TB. Future longitudinal studies incorporating immunological and socioeconomic factors are warranted to better understand the complex interplay that influences the disease trajectory and treatment success in RR-TB.

The present study had several limitations, the first of which was its relatively small sample size, thus limiting statistical power and generalizability of the findings. Second, culture-based confirmation of rifampicin resistance was not performed because molecular diagnostics (GeneXpert MTB/RIF Ultra) were used as the primary reference. Third, the single-center design may not fully represent the broader RR-TB population in Indonesia. Despite these limitations, this study provides valuable insights into the relationship between bacterial burden, clinical severity, and treatment outcomes in patients diagnosed with RR-TB.

## SUPPLEMENTARY INFORMATION

Supplementary information accompanies this article at https://doi.org/10.22207/JPAM.19.4.51

**Additional file**: Table S1.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## AUTHORS' CONTRIBUTION

DC and NMM conceptualized the study. DC, NMM and PBP designed the study. DC and NMM performed data curation, data extraction and laboratory record management. NMM supervision of laboratory procedures, guidance on microbiological analysis. AP supervision of clinical aspects, radiological data analysis, interpretation of clinical correlations. PDE supervision of microbiological methodology, clinical correlation interpretation, patient chart review. AT provided guidance on statistical methodology, validation of analysis, and critical input on data interpretation. DC wrote the manuscript. DC, NMM, AP, PBP, PDE reviewed and edited the manuscript. All authors read and approved the final manuscript for publication.

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None.

## DATA AVAILABILITY

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

## ETHICS STATEMENT

This study was approved by the Health Research Ethics Committee of Dr. Soetomo General Hospital, Surabaya, Indonesia (Ethical Clearance No. 1980/LOE/301.4.2/V/2025).

## INFORMED CONSENT

Written informed consent was obtained from the participants before enrolling in the study.

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