e-ISSN 3123-3384
DOI: https://doi.org/10.12345/jpnar.v2i1.pp24-32
Journal of Pharmaceutical and Natural Resources (JPNAR) June 2026, Volume 2, Issue 1, page 1-7

Drug-Related Problems in Tuberculosis Inpatients: Clinical Relevance and Influence on Hospital Stay Duration

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Submitted : 02 Mei 2026
Published : 30 Juni 2026

ABSTRACT

Pulmonary tuberculosis ranks as the second most widespread infectious disease worldwide and is caused by Mycobacterium tuberculosis. Its treatment requires the use of multiple medications, especially for inpatients and individuals with comorbidities. The greater the number of drugs used, the higher the likelihood of experiencing Drug-Related Problems (DRPs) throughout the treatment process. This study was conducted to examine the DRPs among pulmonary tuberculosis inpatients at RSUD Kota Kendari in 2023. This study employed a retrospective observational design with a descriptive-analytic approach. Study population consisted of all patients diagnosed with pulmonary tuberculosis who were admitted to RSUD Kota Kendari during the study period. The sample was selected using a total sampling technique, including all patients who met the inclusion and exclusion criteria. DRPs identification followed the guidelines of the PCNE version 9.00. From a clinical standpoint, results showed most frequent comorbidity was type 2 diabetes mellitus, and the most common coexisting condition was dyspnea. Regarding pharmacological treatment, 71.6% of patients received first-line anti-TB drugs during the intensive phase, 6.4% were in the continuation phase, and 22.0% were administered the second-line drug, levofloxacin. The most common DRPs were found in domain C1.4 (inappropriate drug combinations) at 94.6%, followed by domain P1.3 (untreated indications) at 2.2%, domain C1.6 (therapy not provided or incomplete despite indication) at 2.2%, and domain P2.1 (potential adverse drug reactions) at 1.1%. The chi-square test indicated no significant correlation between therapeutic outcomes and DRPs ($p = 0.169$); however, a significant relationship was observed between the length of hospital stay and DRP occurrence ($p = 0.00$). These findings underscore the importance of pharmacotherapy monitoring and interdisciplinary collaboration to minimize DRPs, especially in patients receiving complex tuberculosis treatment regimens.

Keywords: Anti-tuberculosis; Clinical Parameters; Drug Related Problems; PCNE; Pulmonary Tuberculosis.

INTRODUCTION

Tuberculosis (TB) remains a major public health concern, particularly in low- and middle-income countries, and continues to be one of the leading causes of death from infectious diseases globally. According to the Global Tuberculosis Report 2023, Indonesia ranks second in the world after India in terms of TB burden, with approximately 1,060,000 new TB cases and 134,000 TB-related deaths reported in 2022 (Kementerian Kesehatan Republik Indonesia, 2024; World Health Organization, 2023). In the Southeast Sulawesi region, TB has consistently ranked among the top ten most prevalent diseases from 2018 to 2020, with Kendari City identified as a high-burden area for pulmonary TB (Saparina et al., 2024; Tosepu et al., 2024).

The primary strategy for TB control involves pharmacotherapy, which requires a combination of multiple anti-tuberculosis drugs taken in appropriate doses over a minimum duration of six to eight months to ensure complete eradication of Mycobacterium tuberculosis (Kementerian Kesehatan Republik Indonesia, 2020; World Health Organization, 2022b). However, the complexity of TB therapy, particularly in hospitalized settings can increase the risk of drug-related problems (DRPs). Contributing factors include polypharmacy, comorbidities, potential drug interactions, and inappropriate prescribing practices (Bektay et al., 2023; Boadu et al., 2024).

DRPs are defined as any event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes (Bektay et al., 2023).

Evidence from previous studies indicates that DRPs can lead to adverse consequences such as prolonged hospital stays, increased healthcare costs, and poorer clinical outcomes, including elevated morbidity and mortality (Achterbosch et al., 2025; Chimeh et al., 2020; Dixon et al., 2024). Consequently, the systematic identification and classification of DRPs is essential to improving therapeutic outcomes and ensuring patient safety. One widely adopted framework for DRP classification is the Pharmaceutical Care Network Europe (PCNE) classification system, which categorizes DRPs into specific domains and subdomains to facilitate comprehensive analysis (Bektay et al., 2023). The implementation of this classification system supports a more precise understanding of DRP causes, thus enabling the development of appropriate pharmaceutical care interventions (Bektay et al., 2023; Pradipta et al., 2023)

Despite the availability of national and global data on TB prevalence, studies specifically addressing DRPs among hospitalized pulmonary TB patients in Indonesia remain limited. Most existing research in the country has focused on general DRP prevalence or treatment adherence but has rarely explored the types and causes of DRPs in hospitalized TB patients using structured and validated tools such as the PCNE classification. Furthermore, there is a notable absence of research from regional hospitals in Eastern Indonesia, such as RSUD Kota Kendari, where healthcare resource limitations and unique patient characteristics may influence prescribing practices and DRP incidence.

This study seeks to address these gaps by evaluating drug-related problems in hospitalized pulmonary TB patients at RSUD Kota Kendari using the PCNE classification system version 9.1. As the first study of its kind in this setting, it aims to identify and categorize DRPs, analyze their underlying causes, and provide recommendations for improved pharmaceutical care. The results are expected to fill critical data gaps at the regional level, offering context-specific insights that can support more rational use of anti-tuberculosis drugs in hospital settings. Ultimately, this study contributes to national efforts in optimizing TB therapy and minimizing the burden of medication-related complications among vulnerable patient populations (Pradipta et al., 2023; World Health Organization, 2022b).

METHODS

- Study Design and Setting

  This study employed a retrospective observational design with a descriptive-analytic approach. The research was conducted at the General Regional Hospital (RSUD) of Kendari City, Southeast Sulawesi, Indonesia. Data were collected from medical records of hospitalized patients diagnosed with pulmonary tuberculosis either TB-drug sensistive and TB-drug resistant between January through December 2023.

- Study Population and Sample

  The study population consisted of all patients diagnosed with pulmonary tuberculosis who were admitted to RSUD Kota Kendari during the study period. The sample was selected using a total sampling technique, including all patients who met the inclusion criteria and exclusion criteria.

  Inclusion Criteria:
  - Hospitalized patients with a confirmed diagnosis of pulmonary tuberculosis either TB-drug sensistive and TB-drug resistant;
  - Patients who received anti-tuberculosis therapy during hospitalization;
  - Complete medical and pharmaceutical records available for review.

  Exclusion Criteria:
  - Patients discharged against medical advice;
  - Patients receiving anti-tuberculosis drugs for prophylactic purposes only.
  - Data Collection

  Patient data were obtained retrospectively through a systematic review of medical records, prescription sheets, laboratory results, and medication administration records. The variables collected included:
  - Demographic data (age, gender);
  - Clinical data (TB diagnosis, comorbidities, length of stay);
  - Pharmacological data (anti-TB regimens, concurrent medications, dosing patterns);

- Documented adverse drug reactions or clinical notes relevant to DRPs;
- Identification and classification of drug-related problems were conducted using the Pharmaceutical Care Network Europe (PCNE) Classification System version 9.0, which provides structured domains for problems, causes, and interventions.

- **Data Analysis**
  Data were analyzed descriptively to determine the frequency and distribution of DRPs, categorized by type and underlying cause based on PCNE v9.0. Categorical variables were presented in frequencies and percentages, while bivariate analyses Chi-square tests were conducted to explore associations between DRP occurrence and clinical parameters (clinical outcomes and length of stay). A p-value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 29.0.

RESULTS AND DISCUSSION

Table 1. Patients Characteristic

Patients Characteristic	n	%
Gender		
Male	65	59,6%
Female	44	40,4%
Age		
19-44	39	35,8%
45-59	30	27,5%
>60	40	36,7%
Comorbidities or coexisting conditions		
Anemia	3	2,4%
Asthma	4	3,2%
Congestive Heart Failure (CHF)	3	2,4%
Type 2 Diabetes Mellitus	16	12,7%
Dyspepsia	7	5,6%
Dyspnea	38	30,2%
Pleural Effusion	4	3,2%
Hemoptysis	28	22,2%
Hypoalbuminemia	3	2,4%
Lower Respiratory Tract Infection (LRTI)	3	2,4%
Length of stay (LOS in days)		
1-6	56	51,4%
7-13	47	43,1%
14-19	3	2,8%
> 20	3	2,8%

Table 1 showed this study involved 109 hospitalized pulmonary tuberculosis (TB) patients, with a higher proportion of male patients (59.6%) compared to females (40.4%). This gender distribution aligns with national and global data, where TB prevalence tends to be higher among males, likely due to behavioral, biological, and social factors that increase exposure risks and delay healthcare seeking in men (Kementerian Kesehatan Republik Indonesia, 2024; World Health Organization, 2023).

The majority of patients were aged over 60 years (36.7%), followed by adults aged 19–44 years (35.8%), and 45–59 years (27.5%). This age distribution indicates a substantial burden of TB among older populations, who often have diminished immune responses and higher risk of comorbidities that complicate TB treatment outcomes (World Health Organization, 2022b; Yagi et al., 2023). The findings support the need for more targeted management strategies in geriatric TB patients.

In terms of comorbidities, dyspnea (30.2%) and hemoptysis (22.2%) were the most frequently reported symptoms or complications, reflecting the advanced disease state or pulmonary complications commonly seen in hospitalized TB patients. These findings are consistent with previous studies showing that respiratory manifestations such as dyspnea and hemoptysis are commonly observed among hospitalized pulmonary TB patients with advanced disease and are frequently accompanied by other pulmonary abnormalities (Lin et al., 2023; Yagi et al., 2023). Dyspnea may not only result from TB infection but also indicate overlapping conditions such as chronic obstructive pulmonary disease or congestive heart failure, which may further complicate treatment and clinical outcomes (Mereškevičiene & Danila, 2025; Yagi et al., 2023).

Diabetes mellitus was the most prevalent non-respiratory comorbidity (12.7%) in this study. This is clinically significant, as diabetes is a known risk factor for poor TB outcomes, delayed sputum conversion, and increased risk of relapse or treatment failure (Boadu et al., 2024). The co-management of diabetes and TB remains a critical challenge and necessitates integrated therapeutic strategies.

Other less frequent but notable comorbidities included dispepsia, pleural effusion, asthma, anemia, hypoalbuminemia, CHF, and lower respiratory tract infections. These conditions may contribute to polypharmacy, thereby increasing the risk of drug-related problems (DRPs), particularly in the context of anti-TB drug interactions and

adverse drug reactions (Bektay et al., 2023; Dixon et al., 2024). For example, hypoalbuminemia can alter the pharmacokinetics of protein-bound drugs, potentially increasing toxicity.

The analysis of length of stay (LOS) revealed that more than half of the patients (51.4%) were hospitalized for 1–6 days, and 43.1% for 7–13 days. Only a small proportion (5.6%) stayed longer than 13 days. Shorter hospital stays may reflect improved early management or resource limitations, though they could also limit opportunities for DRP identification and intervention. On the other hand, longer stays are often associated with treatment complications, DRPs, or severe disease progression.

Compared to previous studies, this research adds valuable insight into the patient characteristics and comorbidity profiles of hospitalized TB patients in a regional Indonesian hospital. The findings emphasize the complex clinical landscape in TB management, particularly in Eastern Indonesia, where the burden of comorbid conditions may be compounded by healthcare access and infrastructure limitations (Bektay et al., 2023; Pradipta et al., 2023).

Tabel 2. Anti-tuberculosis drugs profile

Drug category	Regimen phase	Drug phase	Number of patients (%)
First-line anti-TB drugs	Category 1	Intensive	78 (71,6%)
		Continuation	7 (6,4%)
	Category 2	Intensive	0
		Continuation	0
Second-line anti-TB drugs	-	Levofloxacin	24 (22,0%)

Table 2 showed that the majority of hospitalized pulmonary TB patients received first-line anti-tuberculosis therapy, particularly category 1 drugs in the intensive phase. This aligns with national TB treatment guidelines, which recommend standard short-course regimens for new TB cases (Kementerian Kesehatan Republik Indonesia, 2020; World Health Organization, 2022b). The relatively low number of patients in the continuation phase may suggest that many patients were in the early phase of hospitalization or had newly diagnosed TB requiring initiation of therapy. It could also reflect referral patterns or delays in diagnosis.

Interestingly, a notable proportion of patients (22%) received second-line drugs, with levofloxacin being the primary agent. This finding indicates a possible concern regarding drug resistance or the presence of adverse reactions/intolerance to first-line agents. Levofloxacin, a fluoroquinolone, is recommended in cases of multi-drug resistant TB (MDR-TB) or in patients who cannot tolerate first-line regimens (World Health Organization, 2022a, 2023). The use of second-line therapy in a significant number of patients may reflect either a local increase in resistance patterns or more severe clinical presentations requiring individualized treatment.

Previous studies have also shown a rising trend in fluoroquinolone use for TB management, especially in tertiary care hospitals (Kannabiran et al., 2025; Prakash et al., 2025). Previous studies have also reported an increasing use of fluoroquinolones, particularly levofloxacin, in tuberculosis management for patients with suspected drug resistance, intolerance to first-line anti-tuberculosis drugs, or individualized treatment regimens. Recent evidence has emphasized the importance of optimizing second-line therapy through appropriate drug selection, therapeutic drug monitoring, and careful evaluation of treatment response to improve clinical outcomes (Kannabiran et al., 2025; Prakash et al., 2025; World Health Organization, 2022a). The relatively high proportion of levofloxacin use observed in the present study may therefore reflect differences in patient characteristics, local resistance patterns, referral practices, or clinical decision-making at the hospital level.

The absence of any use of category 2 drugs may suggest a shift in treatment practices where re-treatment cases are managed similarly to new cases, possibly based on updated WHO recommendations that emphasize individualized treatment regimens for all TB cases regardless of treatment history (World Health Organization, 2023). Alternatively, it may reflect underreporting or a lack of documentation in patient records. These findings underline the importance of accurate diagnosis, drug susceptibility testing, and adherence to national TB protocols. Furthermore, the frequent use of levofloxacin should be cautiously monitored to prevent the emergence of fluoroquinolone resistance, which could severely limit future treatment options.

e-ISSN 3123-3384
DOI: https://doi.org/10.12345/jpnar.v2i1.pp24-32
June 2026, Volume 2, Issue 1, page 1-7

Table 3. Identified Potential Drug-Related Problems (DRPs) Among Hospitalized TB Patients

PCNE Code	DRP Category	n	%
P1.3	Untreated symptoms or indication	2	2.2%
P2.1	(Possible) adverse drug event	1	1.1%
C1.4	Inappropriate combination (e.g., drug–drug, drug–herbal, drug–supplement)	88	94.6%
C1.6	Drug not administered although there is an indication	2	2.2%

Table 3 identified a number of potential Drug-Related Problems (pDRPs) among hospitalized tuberculosis (TB) patients using the PCNE V9.0 classification system. The most frequently observed issue was inappropriate drug combinations, including suspected interactions between anti-TB drugs and co-administered medications, herbal remedies, or supplements. Although clinical outcomes were not confirmed, the predominance of this pDRP category, accounting for more than 90% of all cases, raises critical concerns regarding the safety and quality of pharmacotherapy in TB management.

The complexity of TB pharmacotherapy, especially in patients with multiple comorbidities, increases the likelihood of polypharmacy and potential interactions. This pattern is consistent with prior studies, such as those by Yosep & Lestari (2024), which emphasized that improper combinations and incomplete regimens were key contributors to therapeutic failure in TB patients (Bektay et al., 2023; Dixon et al., 2024). Similarly, highlighted that drug–drug interactions in TB patients with chronic comorbidities like diabetes and cardiovascular disease are frequently underreported but clinically significant (Mereškevičiene & Danila, 2025; Ridolfi et al., 2024). In the present study, levofloxacin used in 22% of patients as a second-line anti-TB agent is of particular concern due to its known risk for QT interval prolongation, especially when combined with other QT-prolonging medications.

In addition to drug combinations, other notable pDRPs included the presence of untreated symptoms or indications and instances of incomplete therapy despite an existing medical need. These findings suggest possible lapses in medication reconciliation or clinical assessment during hospital admission. A previous study similarly demonstrated that suboptimal treatment strategies in TB patients, particularly those with concurrent illnesses, can contribute to longer hospital stays and greater risk of complications (Achterbosch et al., 2025; Chimeh et al., 2020; Pradipta et al., 2023).

From a clinical safety perspective, the identification of a potential adverse drug reaction (ADR) in one patient further emphasizes the importance of pharmacovigilance in TB treatment. Although this single observation could not be confirmed due to limited follow-up data, it nonetheless highlights the risk associated with anti-TB drugs which have narrow therapeutic indices. Adverse effects such as hepatotoxicity, dermatologic reactions, and neurotoxic events are well-documented in recent studies. For instance, a prospective cohort in Brazil reported frequent nervous system and cutaneous ADRs, such as peripheral neuropathy, rash, and pruritus during first-line TB therapy (Choi et al., 2022; Chung et al., 2022; Sant'Anna et al., 2022, 2023).

Table 4. Chi-square association analysis of Clinical Parameters and Drug-Related Problems (DRPs) Among Hospitalized Pulmonary Tuberculosis Patients at RSUD Kota Kendari

Clinical Parameter	Category	With DRPs	Without DRPs
Clinical Outcome	Improved	10	0
	Cured	83	16
	Pearson Chi-square p-value		0.169
Length of Hospital Stay (days)	1–6	56	56
	7–12	37	47
	13–19	0	3
	>20	0	3
	Pearson Chi-square p-value		0.000

The bivariate analysis (Table 4) showed no significant association between therapeutic outcomes and the occurrence of drug-related problems (DRPs) among inpatients with pulmonary tuberculosis at RSUD Kota Kendari, with a p-value of 0.169 ($p > 0.05$). This result is consistent with a previous study (Ridolfi et al., 2024), which also found no statistically significant correlation between therapeutic outcomes and DRPs ($p > 0.05$). The lack of correlation may be attributed to other influencing factors on treatment effectiveness beyond the number of DRPs, such as disease severity and the presence of complications.

e-ISSN 3123-3384
DOI: https://doi.org/10.12345/jpnar.v2i1.pp24-32
June 2026, Volume 2, Issue 1, page 1-7

For example, complications related to pulmonary TB, including respiratory failure and hemoptysis, have been reported to negatively impact the likelihood of recovery in patients (Lin et al., 2023). Furthermore, disease severity often correlates more directly with prognosis than DRP incidence alone (Yagi et al., 2023; Zhu et al., 2025).

Meanwhile, association between the length of hospital stay (LOS) and the occurrence of DRPs demonstrates a statistically significant, with a p-value of 0.00 ($p < 0.05$). This finding is supported by Bektay et al., (2023), who reported a significant relationship between LOS and DRPs ($p = 0.001$). The duration of hospitalization in TB patients is influenced by various factors, including comorbidities and adverse drug reactions (Dixon et al., 2024; Sant'Anna et al., 2023). Additionally, drug-drug interactions can prolong hospitalization, especially in patients with comorbid conditions such as diabetes mellitus. The risk of interactions tends to increase when patients are prescribed more than seven medications, as polypharmacy is a well-established risk factor for DRPs and prolonged LOS (Achterbosch et al., 2025; Bektay et al., 2023; Chimeh et al., 2020). These results highlight the clinical importance of early detection and resolution of DRPs, particularly in high-risk populations such as those with comorbidities or polypharmacy, to minimize prolonged hospital stays and optimize TB treatment outcomes

CONCLUSION

In summary, these findings reinforce the need for improved clinical pharmacy services, including systematic medication review, early identification of high-risk drug combinations, and robust ADR monitoring systems. Addressing potential DRPs proactively can enhance therapeutic efficacy, reduce avoidable harm, and ensure safer, more personalized care for TB patients.

ACKNOWLEDGEMENTS

The authors would like to express their sincere gratitude to the management and medical staff of Rumah Sakit Umum Daerah Kota Kendari for granting access to medical records and supporting data collection. We also acknowledge the support from the Faculty of Pharmacy, Universitas Halu Oleo, for academic guidance and administrative assistance during the research process.

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