A HIERARCHICAL CLUSTER ANALYSIS OF CONCURRENT INITIAL ADVERSE EVENTS IN PATIENTS RECEIVING BPAL/BPALM REGIMENS FOR DRUG-RESISTANT TUBERCULOSIS IN LOWER MYANMAR

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ABSTRACT

Myanmar has recently scaled up all-oral BPaL (bedaquiline, pretomanid, and linezolid) and BPaLM (BPaL with moxifloxacin) regimens nationwide for multidrug-resistant or rifampicin-resistant tuberculosis (MDR/RR-TB). While clinically effective, the safety profile of these regimens is characterized by frequent, often concurrent adverse events (AEs). To date, real-world evidence regarding the clustering patterns of these toxicities within the Myanmar context remains limited. We conducted a retrospective analysis of electronic health records from 729 patients with MDR/RR-TB in lower Myanmar, utilizing data from the National Tuberculosis Programme's Open Medical Record System (Open MRS). To characterize early-onset toxicity, analysis was restricted to first-occurrence AEs. We calculated pairwise mean differences (MDs) in time-to-first AE across all event types. These MDs were normalized between 0 and 1 and visualized via heatmaps with 0.1 cut-off intervals. Hierarchical cluster analysis using Euclidean distance and Ward's linkage was applied to identify AE phenotypes based on temporal similarity. Seven distinct AE clusters were identified, with cluster sizes ranging from three to eight events. The most substantial cluster demonstrated multi-system involvement, encompassing palpitations, lower gastrointestinal symptoms, arthralgia, elevated liver enzymes, myalgia, headache, electrolyte disturbances, and QT prolongation. In conclusion, AEs associated with BPaL/BPaLM regimens exhibit distinct multi-systemic clustering patterns, suggestive of a treatment-related syndrome rather than sporadic side effects. These data support a transition toward cluster-based clinical monitoring and integrated safety surveillance to optimize patient management and treatment adherence for patients with MDR/RR-TB.

Keywords: Adverse Events, Heatmap, Hierarchical Cluster Analysis, Tuberculosis, Co-Occurrence

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INTRODUCTION

In 2023, tuberculosis (TB) remained a major global health threat, with an estimated 10.8 million new cases (World Health Organization, 2024). Of these, around 400,000 people (95% UI: 360,000–440,000) developed multidrug- or rifampicin-resistant TB (MDR/RR-TB) (World Health Organization, 2024). The WHO South-East Asia (SEA) Region carried the largest burden, with 45% of global TB cases. Myanmar, a lower-middle-income country in SEA and one of the 30 high-burden nations, faces high TB incidence rates with 558 cases per 100,000 population and MDR/RR-TB at 24 per 100,000 (WHO, 2024). The burden is concentrated in lower Myanmar, Yangon and Bago regions accounted for 55.29% and 8.14% of national MDR/RR-TB cases, respectively (National Tuberculosis Programme, Myanmar, 2025)

Following WHO's 2020 guidelines for drug-resistant TB (DR-TB) treatment, Myanmar's NTP rolled out shorter regimens: the 6–9-month BPaL (bedaquiline, pretomanid, linezolid) starting as a pilot in Yangon in 2022, and the 6-month BPaLM (adding moxifloxacin), expanded nationwide in 2024 (Muhammad & Myint, 2023; National Tuberculosis Programme, Myanmar, 2023). Past studies often reported frequency of each AE without considering how patients experience multiple AEs at the same time in real life (Acuña-Villaorduña et al., 2023; Ali et al., 2023; Berry et al., 2022; Chung et al., 2023; Conradie et al., 2020, 2022; Gualano et al., 2025). Cancer research shows this gap is important, chemotherapy patients have concurrent symptom clusters that correlate strongly over time, like psychoneurological-pain and gastrointestinal groups in breast cancer (Wiranata et al., 2024). No TB studies have mapped these time-based clustering patterns for DR-TB regimens.

To identify non-random groups of co-occurring AEs, data-mining methods such as hierarchical clustering, which have been used in cancer research, are well suited for TB safety monitoring (Everitt, 2011; Wiranata et al., 2024). Combined with heatmaps, these methods clearly display patterns based on time to first occurrence. This approach is appropriate for TB, where prolonged drug exposure may lead to linked toxicities across body systems. However, no study has yet applied this approach to AEs study in DR-TB. This study aims to characterize AEs associated with BPaL and BPaLM regimens in lower Myanmar by examining AEs with similar timing of onset. The specific objectives were to explore patterns of concurrent AEs based on similarities in time-to-first occurrence using heatmap visualization of mean difference of time-to-first occurrence and to identify clusters of co-occurring events through hierarchical cluster analysis. By combining these methods, this study characterizes structured, time-related patterns of treatment-associated toxicities to support enhanced pharmacovigilance and patient safety within the national programme.

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LITERATURE REVIEWS

The BPaL and BPaLM regimens have transformed the management of drug-resistant tuberculosis (DR-TB) by providing shorter, all-oral treatment options with high efficacy for eligible patients with MDR/RR-TB (Conradie et al., 2020; WHO, 2022; World Health Organization, 2024). Evidence from the Nix-TB and ZeNix trials established both the efficacy of these regimens and the importance of linezolid dose optimization for improving tolerability (Conradie et al., 2020,

2022). Their use has expanded in high-burden settings, including Myanmar, where implementation is guided by national program documents and local reports.

Despite these advantages, BPaL and BPaLM are associated with clinically important AEs, particularly peripheral neuropathy, myelosuppression, anemia, optic neuropathy, QT prolongation, and hepatotoxicity (Berry et al., 2022; Conradie et al., 2020). Because most DR-TB safety studies describe AE individually by frequency and severity, concurrent toxicity patterns may be overlooked. Heatmaps and hierarchical clustering may therefore provide additional value by identifying co-occurring adverse event patterns and strengthening pharmacovigilance in routine care (Acuña-Villaorduña et al., 2023).

Conceptual framework of the study

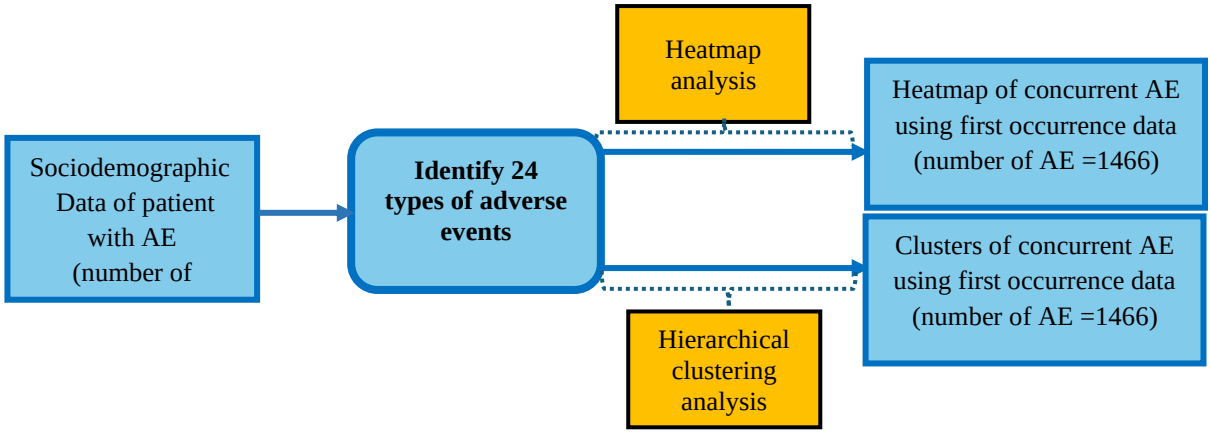

Figure 1 Conceptual Framework

Figure 1 outlines the analytical workflow to identify patterns of AEs among 729 patients receiving BPaL/BPaLM regimens in Lower Myanmar.

RESEARCH METHODOLOGY

Study Design and Data Source

Study Design and Setting

This secondary data analysis utilized data from 14 multidrug-resistant tuberculosis (MDR-TB) treatment centers located in the Yangon and Bago regions of Myanmar, focusing on patients enrolled under the National Tuberculosis Program (NTP) between January 1, 2024, and December 31, 2024, who were treated with either the BPaLM or BPaL regimens.

Clinical Monitoring of AEs

Patients were monitored using a standardized follow-up protocol to ensure early detection of AEs (National Tuberculosis Programme, Myanmar, 2025). For the six-month BPaLM regimen, patients attended visits at week 2 and monthly until treatment completion. For BPaL, follow-up was conducted at week 2 and monthly thereafter for up to 9 months, depending on treatment duration. At each visit, clinicians assessed signs and symptoms through physical examination and performed routine laboratory investigations to detect treatment-related toxicities.

Definition and Classification of AEs

AEs were defined according to NTP clinical monitoring guidelines as an adverse event as any untoward medical occurrence that may present during treatment with a pharmaceutical product, but which does not necessarily have a causal relationship with the treatment. For the analysis, only the first occurrence of each adverse event per patient was included. This approach prevents overrepresentation of frequently recurring events and enhances comparability across patients.

Recording of AEs in Myanmar NTP

OpenMRS is an open-source electronic medical record system widely used in resource-limited settings (National Tuberculosis Programme, Myanmar, 2024). The collected data from databases

include comprehensive information such as patient ID, age, sex, dates and times of treatment started, region, regimen, site of infection, BMI, comorbid diseases, investigation results and AEs.

Data Extraction and Data Collection

All relevant demographic characteristics, clinical parameters, and AEs data were systematically extracted from the facility-based OpenMRS database using the integrated "Reports" module. Specifically, comprehensive clinical and demographic information was retrieved via the "Advanced Report" feature, while detailed AEs profiles were obtained through the "Side Events Patient List." Data extraction was completed on September 30, 2025, across all 14 participating treatment sites.

Data Cleaning and Restructuring

Data from OpenMRS were extracted from 14 treatment sites, where time variables were recorded in different formats. A standardized data cleaning process was therefore implemented in R. All date fields were converted to a uniform format, and invalid values were corrected. Logical checks were performed to ensure that adverse event dates occurred after treatment initiation and within the follow-up period. The dataset was then reshaped from wide to long format, with each row representing one adverse event per patient. Duplicate records were removed based on patient ID, event type, and event date.

Sample Size

We used all individuals' data in our interest population. The information from this study directly represented the population. This was not inferential statistics. Hence, the sample size calculation was omitted.

Data Preparation and analysis

Baseline comorbidities, including anemia, chronic liver disease, and chronic kidney disease, were reviewed to distinguish treatment-emergent AEs from pre-existing conditions and reduce confounding. For each adverse event, time from treatment initiation to first occurrence was calculated, and mean time to first event was estimated across patients. Pairwise temporal proximity was assessed using a mean difference matrix based on the absolute differences in mean onset times, which was normalized to a 0–1 scale and displayed as a heatmap.

Hierarchical Clustering and Interpretation

Agglomerative hierarchical cluster analysis using Euclidean distance method was applied to the normalized MD matrix to identify nested clusters of AEs with similar timing of onset. Distance between AE pairs was defined by their normalized mean difference called standardized mean difference (SMD). SMD quantified between variable differences on a common scale. Per established conventions, SMD < 0.1 indicates negligible differences (Andrade, 2020; Cohen et al., 2019; Normand et al., 2001). Thus, lower SMD values signified greater temporal similarity between AEs, forming the basis for hierarchical clustering dendrogram interpretation. To enhance clinical interpretability, cluster interpretation focused on AE pairs with a normalized MD < 0.1, representing toxicities that manifested in close temporal proximity. Clusters were defined based on aggregation of MDs under 0.1 dendrogram structure derived from hierarchical cluster analysis.

Study Outcome

The demographic characteristics were described using descriptive statistics in table. The primary outcome was the identification of temporal clusters of concurrent AEs associated with BPaL/BPaLM regimens. Unlike frequency-based co-occurrence, this methodology characterizes clusters based on the synchronized timing of onset. This approach provides a robust framework for identifying clinically meaningful patterns of multi-systemic toxicity, ultimately informing targeted pharmacovigilance and patient monitoring strategies under programmatic conditions.

RESEARCH RESULTS

Descriptive Overview

A total of 729 patients experienced at least one adverse event. Table 1 shows the basic characteristics of patients who experienced AEs. The most frequently reported AEs included

nausea, vomiting, peripheral neuropathy, elevated liver enzymes, and dizziness. Less frequent events include QT prolongation and electrolyte disturbances.

Table 1 The basic characteristics of patients with at least one AE

Variable	**N = 729**[1]
Age	40.0 (29.0, 53.0)
Sex	
Female	287 (39%)
Male	442 (61%)
Body Mass Index (BMI)	
<18.5 (Underweight)	432 (59%)
≥25 (Overweight)	39 (5.3%)
18.5–24.9 (Normal)	258 (35%)
Regimen	
BPaL Regimen	98 (13%)
BPaLM Regimen	631 (87%)
Region	
Bago	9 (1.2%)
Yangon	720 (99%)
Site of TB infection	
Both	19 (2.6%)
Extrapulmonary tuberculosis	5 (0.7%)
Pulmonary tuberculosis	705 (97%)
[1]Median (Q1, Q3); n (%)	

Heatmap of Temporal Architecture of Adverse Event Onset (First Occurrence)

Figure 2 illustrates an overview of the temporal proximity of occurrence among 24 AEs. This heatmap is scaled from 0 (red) to 1 (blue), representing smaller to larger SMD between AE pairs, and illustrates a clear temporal gradient in the occurrence of toxicities. A large, high-density red zone (SMD < 0.1) is concentrated in the lower-right quadrant of the matrix, indicating close temporal occurrence among multiple AEs. This region includes cardiac, hepatic, musculoskeletal, and systemic symptoms, suggesting that these events tend to manifest within a similar time window during treatment. In contrast, the upper-left quadrant is characterized by predominantly blue and yellow tones (SMD > 0.6), reflecting larger time differences. AEs such as hypothyroidism, hearing disturbance, and leukopenia appear temporally separated from the main clusters, indicating delayed or isolated onset relative to other toxicities.

Overall, smaller mean time differences were more frequently observed among AEs within related physiological domains, whereas larger mean time differences were common between events

across different systems. These temporal patterns identified in the heatmap were subsequently examined using clustering and network analyses to further characterize the structure of adverse event occurrence.

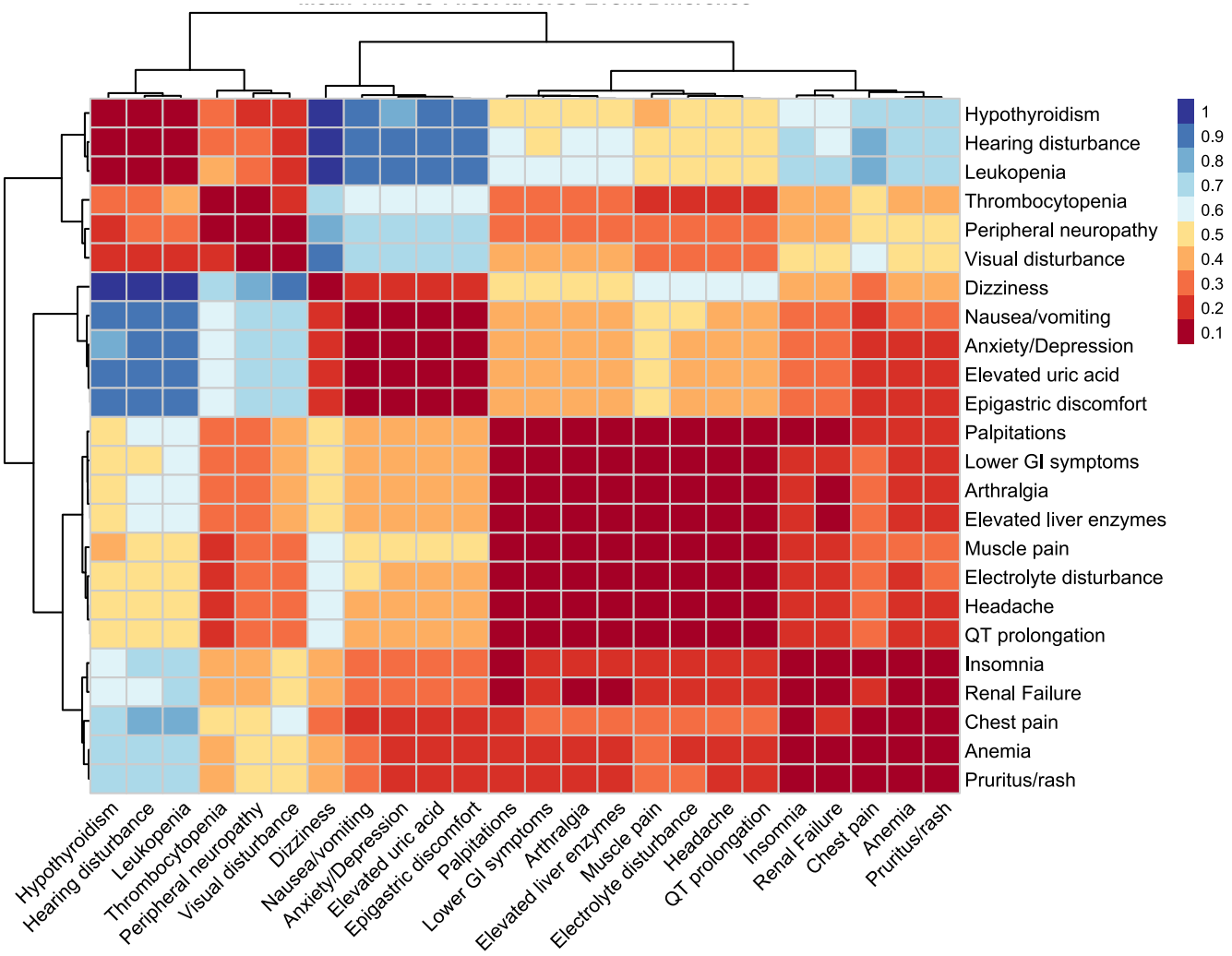

Figure 2: Heatmap with hierarchical clustering showing concurrent AEs based on first-occurrence data. A large, high-density red zone (SMD < 0.1) is concentrated in the lower-right quadrant of the matrix, indicating close temporal occurrence among multiple AEs.

Seven adverse-event clusters were identified. Cluster 1 included pruritus/rash, anemia, chest pain, renal failure, and insomnia. Cluster 2 was the largest and included palpitations, lower gastrointestinal symptoms, arthralgia, elevated liver enzymes, muscle pain, headache, electrolyte disturbance, and QT prolongation. Cluster 3 included arthralgia, elevated liver enzymes, and renal failure. Cluster 4 included insomnia, renal failure, and palpitations. Cluster 5 included epigastric discomfort, elevated uric acid, anxiety/depression, and nausea/vomiting. Cluster 6 included visual disturbance, peripheral neuropathy, and thrombocytopenia. Cluster 7 included leukopenia, hearing disturbance, and hypothyroidism. These clusters suggest that AEs during BPaL and BPaLM treatment often occur in coordinated multisystem patterns rather than as isolated events.

DISCUSSION

This study analyzed 729 patients with MDR/RR-TB in lower Myanmar, where 87% received the BPaLM regimen and 59% were underweight. The cluster analysis identified several clinically meaningful patterns of AEs among patients receiving MDR/RR-TB treatment. Cluster 1 in this

study showed an acute systemic–hematologic toxicity pattern with renal involvement that may reflect concurrent dermatologic, hematologic, and renal stress during treatment (Acuña-Villaorduña et al., 2023; Cohen et al., 2019). Cluster 2 represented the largest and most complex cluster and indicated a major multisystem toxicity cluster involving gastrointestinal, neurologic, hepatic, metabolic, and cardiac manifestations. Similar multisystem AEs have been reported in patients receiving bedaquiline- and linezolid-containing regimens, highlighting the need for integrated clinical, biochemical, and electrocardiographic monitoring during treatment (Conradie et al., 2020; Hasan et al., 2023; Wasserman et al., 2022). Cluster 3 suggested synchronized hepatic and musculoskeletal toxicity possibly mediated by shared inflammatory or metabolic mechanisms (He et al., 2025). Cluster 4 represented a renal-systemic symptom cluster that may reflect interactions between renal dysfunction and systemic manifestations such as sleep disturbance and cardiovascular stress. Cluster 5 formed a neuro-gastrointestinal-metabolic symptom complex that may negatively affect treatment tolerability and patient adherence, consistent with previous studies reporting frequent gastrointestinal and psychological AEs during treatment with all-oral drug-resistant tuberculosis regimens (Muhammad & Myint, 2023; Walker et al., 2019). Cluster 6 represented a hematologic-neurologic toxicity pattern consistent with the well-recognized AE profile of linezolid-containing regimens (Oktaviani et al., 2025; Wasserman et al., 2022). Finally, Cluster 7 showed delayed or independent toxicities that may emerge later during treatment or through distinct biological mechanisms(Lan et al., 2020; Nguyen et al., 2023).

These findings show the value of examining AEs as co-occurring patterns rather than as separate outcomes. Many pharmacovigilance studies assess each adverse event individually, which may miss important relationships between toxicities (Alexandru et al., 2025; Gualano et al., 2025). In contrast, clustering methods can identify groups of AEs that occur together and provide a clearer picture of treatment-related toxicity (Sarangdhar et al., 2016; Uesawa, 2025; Zhong et al., 2016). Applying hierarchical clustering to MDR/RR-TB data is therefore a useful way to detect these patterns in real-world settings. This may help clinicians improve monitoring and manage toxicities earlier, especially in resource-limited settings.

Strength and Limitation

This study has several strengths. It used real-world data from 729 patients in the Myanmar National TB Programme, making the findings relevant to routine MDR/RR-TB care. It also applied a novel clustering approach to identify groups of co-occurring AEs, providing a more complete picture of treatment toxicity. However, the retrospective design and use of routine data may have led to missing or inconsistent AE reporting. Causal links between treatment and AE clusters could not be established, and some clinical details were unavailable In addition, the findings may have limited generalizability to all MDR/RR-TB patients in Myanmar.

CONCLUSIONS

This study identified seven temporal clusters of AEs among MDR/RR-TB patients treated with BPaL and BPaLM, showing that toxicities often occur in related patterns rather than as isolated events. The main multisystem toxicity cluster highlights the need for integrated clinical, biochemical, and cardiac monitoring during treatment. Other clusters with delayed or specific toxicities also indicate the need for continued surveillance throughout therapy. These findings provide real-world evidence that cluster-based monitoring may improve early detection of AEs, support proactive patient management, and strengthen pharmacovigilance in Myanmar and other resource-limited settings.

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