Journal of Clinical Tuberculosis and Other Mycobacterial Diseases 39 (2025) 100515

Contents lists available at ScienceDirect

Journal of Clinical Tuberculosis and Other Mycobacterial Diseases

journal homepage: www.elsevier.com/locate/jctube

Adverse drug reactions and contributing factors in patients with drug-resistant tuberculosis: A 7-year retrospective cohort study in Addis Ababa, Ethiopia☆

Bisrat Solomon [a,*], Yimtubezinash Woldeamanuel [a], Tigest Ajeme [a], Mbazi Senkoro [b], Tsegahun Manyazewal [a]

[a] Addis Ababa University, College of Health Sciences, Center for Innovative Drug Development and Therapeutic Trials for Africa (CDT-Africa), Addis Ababa, Ethiopia
[b] National Institution for Medical Research, Muhimbili Centre, Dar es Salaam, Tanzania

ARTICLE INFO

Keywords:
Adverse drug reaction
Drug-resistant tuberculosis
Treatment outcome
Ethiopia

ABSTRACT

Background: Drug-resistant tuberculosis poses a major global public health threat, with adverse drug reactions complicating treatment and contributing to mortality. In Ethiopia, although many patients with drug-resistant tuberculosis are receiving treatment, studies on adverse drug reactions and their contributing factors remain limited. This study aimed to assess the incidence of adverse drug reactions and contributing factors in patients on drug-resistant tuberculosis treatment in Addis Ababa, Ethiopia.

Methods: A facility-based, retrospective cohort study was conducted on patients with drug-resistant tuberculosis who were followed up in two major drug-resistant tuberculosis treatment sites, St. Peter's Specialized Hospital and the ALERT Comprehensive Specialized Hospital, in the years of 2017 to 2023. Records of the patients were reviewed throughout their treatment time. Information on any adverse drug reaction diagnosis, laboratory findings, clinical observations, type of second-line regimen, type and nature of the drug-resistant tuberculosis, presence of comorbidities such as Human Immune deficiency Virus, hypertension, diabetes mellitus, chronic obstructive pulmonary diseases, and asthma, and sociodemographic characteristics were abstracted from patients' charts and registries. The World Health Organization – Uppsala Monitoring Center (WHO-UMC) system was employed for standardized causality assessment of adverse drug reactions. Multivariate Cox regression analysis was employed to identify factors associated with adverse drug reactions. Survival among predictor variables was assessed using Kaplan-Meier (KM) curves. Adjusted hazard ratios (AHR) with their corresponding 95 % confidence intervals (CI) were estimated, and statistical significance was declared for a p-value < 0.05.

Result: A total of 292 patients with drug-resistant tuberculosis were included. The overall incidence of adverse drug reaction was 8.10 per 100 person-month (PM) (95 % CI: 7.02–9.36) during a total follow-up time of 2294 months. The most frequently reported adverse drug reactions were gastrointestinal disturbance (31.9 %), followed by peripheral neuropathy (21.9 %), and arthralgia (17.5 %). Factors associated with adverse drug reactions were hospitalization (AHR = 1.53, 95 % CI: 1.10–2. 13), baseline anemia (AHR = 1.58, 95 % CI: 1.16–2.17), the age group of 25–49 years (AHR = 1.53, 95 % CI: 1.05–2.21), and age greater than or equal to 50 years (AHR = 1.87, 95 % CI: 1.19–2.93). Good treatment outcome was observed in 76 % of cases.

Abbreviations: ADR, Adverse drug reaction; AHR, Adjusted Hazard ratio; Bdq, Bedaquiline; BPal, Bedaquiline Pretomanid, Linezolid; Cm, Caperomycin; CHR, Crude Hazard Ratio; Cfz, Clofazamine; CI, Confidence interval; Cs, Cycloserine; DRTB, Drug Resistant Tuberculosis; E, Ethambutol; Eto, Ethionamide; HIV, Human Immuno deficiency Virus; H, Isoniazid; Km, Kanamycin; KM, Kalpan Meier; Lfx, Levofloxacin; Linezolid, Lzd; LTFU, Loss To Follow Up; Mfx, Moxifloxacin; MDRTB, Multi Drug Resistant Tuberculosis; NTP, National Tuberculosis Program; PM, Person Month; Pto, Prothionamide; RM, Regimen Modification; RRTB, Rifampicin Resistant Tuberculosis; SAE, Serious Adverse Event; TVC, Time Varying Covariate; UMC, Uppsala Monitoring Center; WHO, World Health Organization; Z, Pyrazinamide.

☆ This article is part of a special issue entitled: 'drug-resistant Tuberculosis' published in Journal of Clinical Tuberculosis and Other Mycobacterial Diseases.

* Corresponding author at: Addis Ababa University, College of Health Sciences, Center for Innovative Drug Development and Therapeutic Trials for Africa (CDT-Africa), P.O. Box 9086 Addis Ababa, Ethiopia.

E-mail addresses: bisrats747@gmail.com (B. Solomon), yimtubezenash.wamanuel@aau.edu.et (Y. Woldeamanuel), tsegahun.manyazewal@aau.edu.et (T. Manyazewal).

https://doi.org/10.1016/j.jctube.2025.100515

Available online 5 March 2025

Conclusion: In this study involving patients with drug resistant tuberculosis, over half of the participants encountered at least one adverse drug reactions. Patient admission, baseline anemia, and older age were identified as major factors associated with adverse drug reaction during multidrug resistant tuberculosis treatment. Particular emphasis should be placed on these susceptible groups to facilitate early prediction, prompt management, and the formulation of appropriate treatment regimens that address adverse drug reactions effectively.

1. Background

Tuberculosis (TB) is a major public health problem and is one of the leading causes of death from a single infectious disease [1]. Globally, in 2022, 10.6 million people were diagnosed with TB and resulted in 1.3 million deaths [2]. According to the 2023 World Health Organization (WHO) African region TB report, Africa accounted for 23 % of TB cases and 31 % of TB-related deaths. Ethiopia is still one of the 30 high-burden TB countries and the emergence of drug resistant TB (DR-TB) is imposing an additional burden to the TB control effort [3,4]. Unlike the 6 month regimen for drug susceptible TB, multidrug-resistant (MDR) TB treatment involves complex second line drugs which require long term regimens with higher toxicity profile [5]. WHO defines adverse drug reactions (ADRs) as harmful, unintended reactions to medicines used at therapeutic doses [6]. The global prevalence of ADRs during DR-TB treatment varies widely, ranging from 69 % to 96 %. In high-burden MDR-TB countries such as Pakistan, the prevalence was reported to be 72.4 %, while in Human Immunodeficiency Virus (HIV) /TB co-endemic countries like Angola it was 82.9 % [7–9]. The most commonly reported ADRs include gastrointestinal (GI) symptoms, arthralgia, psychiatric disorders, and hearing loss or vestibular disorders [10–14]. The toxicity of MDR-TB regimens contributes to poor treatment outcomes, life threatening conditions, and death [5]. Identifying factors associated with ADRs, such as age, sex, smoking, alcohol consumption, substance abuse, nutritional status, anemia, comorbidities, and a prior TB history is critical to improving patient outcomes [13,15–17].

In Ethiopia, the national guideline on TB was revised in 2021 to incorporate new global recommendations on diagnostic, preventive, and treatment modalities. The treatment modalities include all-oral Bedquiline-containing Shorter regimens, BPal (Bedaquiline, pretomanid, linezolid) regimens under operational research, and modifications on longer regimens [18]. There are few studies done on ADRs and adverse effects of DR −TB treatment in Ethiopia [16,19,20]. In a study done in Addis Ababa, adverse event associated with MDR TB treatment was high, 92 % of patients had at least one event during treatment [20]. After the introduction of Bedaquiline (Bdq) and Delamanid (Dlm) through the Ethiopian National TB Programme (NTP) in 2016, one study has shown an early result of adverse effects to be 58.8 % [19]. There is no recent study that shows ADRs during DR-TB treatment. Moreover, studies in Ethiopia have focused on specific adverse events or regimens, with results showing a wide discrepancy among each other [21,22]. Therefore, this study aims to assess the incidence rate of ADRs and associated factors in patients on DR-TB treatment in Addis Ababa, Ethiopia.

2. Methods

2.1. Design and setting

A facility-based retrospective cohort study was conducted using secondary data obtained from two hospitals in Addis Ababa, Ethiopia. Addis Ababa is the capital city of Ethiopia, with a population of 5.7 million [23]. The selected hospitals were St. Peter's Specialized Hospital and ALERT Comprehensive Specialized Hospital (ALERT), located in Addis Ababa, Gulele sub-city, and Kolfae Keraniyo sub-city, respectively, and has a high TB patient load. St. Peter Specialized hospital is the first DR-TB treatment site in Ethiopia and has served as a national referral center [20]. ALERT hospital started MDR TB treatment in 2011 and was one of the first centers to provide treatment using new and repurposed anti-TB drugs in Ethiopia [19].

2.2. Sample size estimation

The sample size was determined using a single population-proportion formula. The proportion of ADR in previous study was 72.4 % [8], with a 95 % CI, 5 % margin of error, and adding a 10 % non-response rate, the final sample size was 292. Between 2017 and 2023, St. Peter's Tuberculosis Specialized Hospital had 534 DR-TB patients, while ALERT Hospital had 352 DR-TB patients. Proportional allocation was applied to each hospital, which resulted in 176 patients from St. Peters Specialized Hospital and 116 patients from ALERT Hospital. A systematic random sampling technique was used to select study participants.

At St. Peter's Hospital, with 534 patients, the sample size was 176, and the sampling interval (K) was 534/176 = 3. The 3rd patient on the DR-TB clinic registry was selected first, and then every 3rd patient until 176 participants were reached. A similar procedure was applied at ALERT Hospital, where 352 DR-TB patients were on the registry, giving K = 352/116 = 3. Every 3rd patient was selected, starting with the third, until 116 participants were reached. Patients who did not fulfill the inclusion criteria were skipped, and the sampling continued until the total of 292 was achieved.

2.3. Participants

All patients who were treated for DR-TB were the source population. The study populations were patients who were treated with DR-TB at the selected public hospitals in Addis Ababa in the years 2017 to 2023. The inclusion criteria were bacteriologically confirmed DR-TB patients of any age who were treated with second line regimen from 2017 to 2023. Bdq and Dld were introduced to ALERT and St. Peter Specialized Hospital in 2017, and patient charts from 2017 to 2023 were reviewed to include patients taking these medications. The exclusion criteria was patients whose charts were incomplete for ADR data, including missed follow-ups for major laboratory investigations recommended in the Ethiopian National TB treatment guidelines. In addition, patients who had confirmed chronic kidney disease, hepatitis, hypothyroidism, and hearing loss before the initiation of DR-TB treatment were excluded.

2.4. Variables

The dependent variable was ADR. Independent variables were socio-demographic factors such as age, sex, residence, marital status, and educational level. Clinical factors included site of TB, TB registration group, Body Mass Index (BMI), anemia at presentation, treatment regimen, concomitant drug intake, HIV co-infection, drug resistance type, hospitalization, and other co-morbidities such as hypertension, diabetes mellitus, chronic obstructive pulmonary diseases and asthma.

2.5. Definitions

The key scientific terms, measurements, and outcome variables in the study are summarized as operational definitions in Table 1.

2.6. Data collection

A standardized data abstraction form adapted from the WHO guidelines and previous literature was used to collect secondary data

Table 1
Operational definitions of scientific terms, measurements, and outcome variables in the study.

Term	Operational definition
GI disturbances	Nausea, vomiting, abdominal pain, diarrhea, reflux hematemesis, melena, or positive occult blood in stool analysis or by endoscopy [16].
Hepatotoxicity	A 3-fold increase in serum transaminases with symptoms or a 5-fold increase without symptoms.
Acute kidney injury	An increase in creatinine by 1.5–2.0 mg/dl above baseline during treatment.
Hypothyroidism	A TSH level > 10 mIU/L after 3 months on DR-TB treatment [18].
Anemia	Hemoglobin < 12 mg/dl for females and < 13 mg/dl for males [24].
Peripheral neuropathy	Tingling, numbness, or burning in the trunk or extremities, as diagnosed by a clinician [25].
Hypokalemia	A serum potassium level < 3.0 mEq/L
Psychiatric disturbances	Anxiety, hallucinations, insomnia, depression, suicidal ideation, or seizures [7].
Hearing loss or vestibular disorders	Hearing loss or vestibular disorders as confirmed by audiometry or clinical diagnosis [18].
Visual disturbances	Vision loss, poor vision, or pain, as diagnosed by a physician [25].
Arthralgia	Pain, swelling, or stiffness in joints or an elevated uric acid level (>6 mg/dl in women or > 7 mg/dl in men) [8].
Body mass index	Severely underweight (<16.5), underweight (16.5–18.49), normal (18.5–24.9), and obese (≥30 kg/m^2) [26].
Cured	A patient who completed treatment according to national policy with three or more consecutive negative cultures 30 days apart after the intensive phase or at the end of a longer regimen.
Treatment completed	A patient who finished treatment without meeting the criteria for failure or cure.
Treatment failure	A regimen is permanently changed or terminated.
Died	A patient who passed away during treatment.
Lost to follow-up	A patient who either did not start treatment or had treatment interruption for 2 or more consecutive months.
Not evaluated	A patient with no assigned treatment outcome [18,27].
Good treatment outcome	A patient completes treatment or is cured
Poor treatment outcome	A patient with treatment failure, death, or loss to follow-up [4].
Serious adverse events	Events leading to death, life-threatening experiences, hospitalization, significant disability, congenital anomalies, or requiring intervention to prevent severe outcomes [28].

from the patients' charts. Data on demographic, clinical, ADRs, and treatment outcomes was collected. The medical records of those treated for DR-TB were obtained from the DR-TB clinic registries at the two study sites. A unique identifier was given, and the patient's name was not recorded on the data collection form. Three data collectors who had a first degree in medicine and with a previous experience collecting such data were recruited. One-day training was given on data collection. According to the national TB guideline monitoring schedule, clinical evaluation, laboratory tests, and ECG were done monthly and based on specific clinical indication [18]. Clinical evaluation and Ischaria test was done for visual disturbance, while hearing loss was assessed clinically and using audiometer. Laboratory test results, such as complete blood count, liver function tests, renal function tests, thyroid function tests, serum electrolytes, serum uric acid, hepatitis, and HIV were collected as available. Details of ADRs were recorded, which could be laboratory test results or clinical reports developed by the clinician handling the patient. Assessment of ADRs was done at each scheduled and unscheduled visits. An event diagnosed by a clinician based on one laboratory result was considered sufficient for the diagnosis of an ADR and the WHO UMC (Uppsala Monitoring Center) system for standardized causality assessment was used [8]. The principal investigator has done supervision daily and closely with data collectors from each site. The data was checked for accuracy, completeness, consistency, coding errors, out-of-range values, clarity, missing values and the errors were corrected based on the finding.

2.7. Data analysis and interpretation

Collected data was cleaned and entered using EPI Data version 3.1, and was exported to STATA version 17.0. Descriptive statistical methods were presented using frequency and percentages for categorical variables, mean, and SD (standard deviation) for continuous variables. Person-time incidence rate (IR) was used for the occurrence of ADRs. The Kaplan Meier (KM) curve was used to evaluate survival among independent variables. Before running the Cox regression model, the proportional hazard assumption was checked. Graphical presentation, Schoenfeld residual test, and/or the time-varying covariates (TVC) were used in the multivariable Cox regression for final decision-making, and variables with P-value > 0.05 were considered as fulfilling the assumption. Variables with a p-value below 0.25 in the bivariable Cox regression model were included in multivariable Cox regression model. Additionally, crude and adjusted hazard ratios with their 95 % confidence intervals (CI) were estimated, and p-values less than 0.05 indicated statistical significance in the multivariable regression. The backward elimination method was used.

3. Results

3.1. Socio-demographic and clinical characteristics

A total of 292 DR-TB patients, 176 from St. Peter specialized Hospital and 116 from ALERT Hospital, were included in the study. Fig. 1 demonstrates the process involved in the selection of the study participants from the study sites.

Majority of the patients (60.27 %) were from St. Peter Specialized Hospital. The mean age with (SD) was 34 (±13.64) years. More than half of the patients were male (55.14 %), while 45.55 % were married. Majority of the patients were from urban areas (82.88 %), and only 38.01 % had primary education. **(**Table 2**).**

More than three-fourths (77.05 %), of the patients had pulmonary TB, and 59.25 % were treated with long-term regimens with newer drugs. 96.23 % of the patients had RR TB, 22.95 % had HIV co infection, and 15.75 % had other comorbidities **(**Table 3**).**

3.2. Incidence and implications of adverse drug reactions

The overall incidence of ADRs was 8.10 per 100 persons-month (PM) (95 %CI: 7.02, 9.36) observation. Total follow-up time was 2294 months. The overall median survival time was 8 months. The minimum follow-up time was 1 month, while the maximum follow-up time was 27 months. The KM curve was used to evaluate survival among independent variables **(**Fig. 2**).**

A total of 186 (63.69 %) DR-TB patients initially free from any ADR developed at least one event during treatment**.** The most common ADR was gastrointestinal disturbance (31.85 %), followed by peripheral neuropathy (21.92 %), arthralgia (17.47 %), visual disturbance (16.44 %), and psychiatric disturbances (8.22 %). Less frequently observed ADRs were anemia (4.79 %), hearing loss (3.42 %), hepatotoxicity (3.08 %), prolonged QT interval (1.71 %), reaction at the injection site (0.68 %), nephrotoxicity (0.68 %), hypothyroidism (0.34 %), and myelosupression (0.34 %) **(**Table 4**).**

Drugs identified during treatment were Levofloxacin (Lfx), Moxifloxacin (Mfx), Bedaquiline (Bdq), Linezolid (Lzd), Clofazimine (Cfz), Cycloserine (Cs), Caperomycin (Cm), Prothionamide (Pto), Pyrazinamide (Z), Ethambutol (E), Isoniazid (H), Ethionamide (Eto), and Kanamycin (Km). GI disturbances such as nausea and vomiting and anemia were the most common cause of serious adverse events. Lastly, 76.03 % of the patients had a good treatment outcome, while 19.52 % had a poor treatment outcome, and 4.45 % were not evaluated.

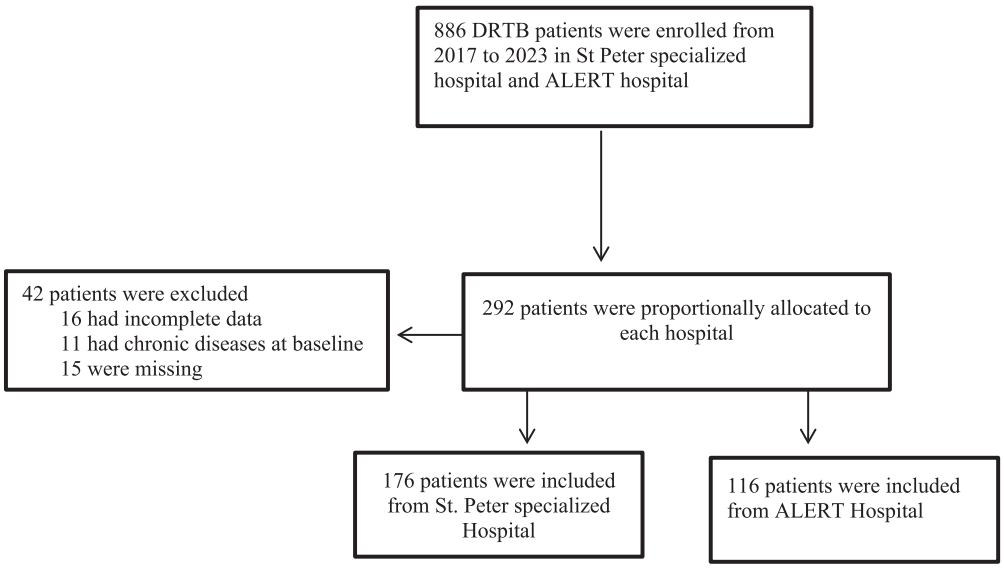

Fig. 1. Flow chart showing selection of DR-TB patients on treatment in selected public hospitals in Addis Ababa, Ethiopia from 2017 to 2023.

Table 2
Socio-demographic characteristics of patients on DR-TB treatment in public hospitals in Addis Ababa, Ethiopia, from 2017 to 2023 (N = 292).

Variables	N (%)
Health facility	
St. Peter Specialized Hospital	176 (60.27)
hh	116 (39.73)
Age	
1–25	83(28.42)
25–49	157(53.77)
≥ 50	52 (17.81)
Sex	
Male	161 (55.14)
Female	131 (44.86)
Residence	
Urban	242(82.88)
Rural	50(17.12)
Marital status	
Single	130 (44.52)
Married	133 (45.55)
Divorced/Separated	18 (6.16)
Widowed	11 (3.77)
Education	
No formal education	65 (22.26)
Primary education	111 (38.01)
Secondary education	77 (26.37)
Diploma and above	39 (13.36)

3.3. Factors associated with adverse drug reactions

To identify factors associated with ADRs, Cox proportional regression model was used. Before fitting the covariate into the model, the proportional hazard assumption was checked graphically, using the Schoenfeld test, and or using TVC. Bivariate analysis showed that age, HIV co-infection, concomitant medication use, registration group, regimen, patient admission (hospitalization), and anemia were associated with ADRs (Table 3). In the multivariable Cox regression, three variables were significantly associated with ADRs. Patients aged 25–49 (AHR = 1.53, 95 %CI: 1.05–2.21), age ≥ 50 years (AHR = 1.87, 95 %CI: 1.19–2.93), patient admission status (AHR = 1.53, 95 %CI: 1.10–2.13) and anemia at presentation (AHR = 1.58, 95 %CI: 1.16–2.17) were statistically significant **(**Table 5**).**

Table 3
Clinical characteristics of patients on DR-TB treatment in public hospitals in Addis Ababa, Ethiopia, from 2017 to 2023 (N = 292).

Variables	N (%)
BMI	
Severely underweight	89 (30.48)
Underweight	51 (17.47)
Normal	144 (49.32)
Obese	8 (2.74)
HIV co-infection	
Yes	67 (22.95)
No	225 (77.05)
Other comorbidities	
Yes	46(15.75)
No	246(84.25)
Registration group	
New	132 (45.21)
Relapse	109 (37.33)
Treatment after failure or LTFU	51 (17.47)
Drug resistance type	
RRTB	281(96.23)
MDR TB	8 (2.74)
Pre XDR TB	3 (1.03)
Concomitant medication use	
Yes	88 (30.14)
No	204 (69.86)
Site of DRTB	
Pulmonary TB	225 (77.05)
Extra pulmonary TB	39 (13.36)
Disseminated TB	28 (9.59)
Treatment regimen	
Long term regimen	31 (10.62)
Long term regimen with new drug	173 (59.25)
Short term regimen	88(30.14)
Patient admission	
Yes	70 (23.97)
No	222 (76.03)
Anemia	
Yes	71 (24.32)
No	221 (75.68)
Treatment completion status	
Good treatment outcome	222 (76.03)
Poor treatment outcome	57 (19.52)
Not evaluated	13 (4.45)

Short term regimens Km-Mfx-Pto-Cfz-Z-HH-E or Bdq-Lfx-Cfz-Z-E Hh-Eto.
Fully oral long term regimen Bdq-Lfx/Mfx-Lzd-Cfz-Cs or Bdq-Lfx/Mfx-Lzd-Cfz-Cs-Dld.
Long term regimen Lfx-Cm-Pto/Eto-Cs-Z.

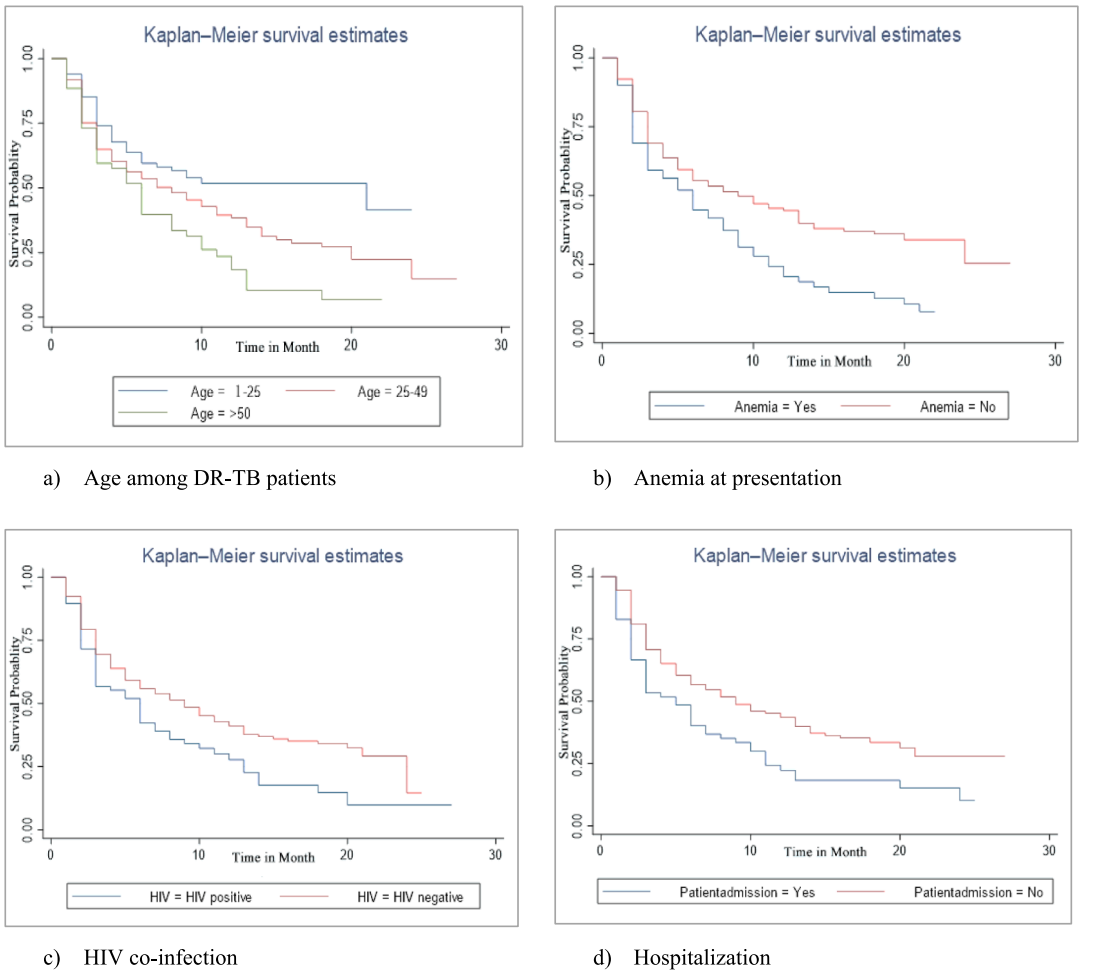

Fig. 2. Kaplan-Meier survival curve for a) age, b) anemia at presentation, c) HIV co-infection, and d) hospitalization among DR-TB patients in selected public hospitals in Addis Ababa, Ethiopia, from 2017 to 2023.

4. Discussion

In this study, the incidence of ADR was 8.10 per 100 person-month observation. This result is slightly comparable with studies done in Ethiopia and Uganda, which had an incidence of 5.79 and 5.56 per 100 Person-month observations, respectively [16,29]. However, it is much higher than a study in Georgia, which had an incidence of 1.16 per 100 Person-month observations [30]. There is variation between these studies due to differences in the definition of a specific ADR, the type of adverse event included (such as severe or non-severe, symptomatic or laboratory-confirmed), and variations in the type of regimen used during treatment.

Gastrointestinal disturbance was the most common ADR, occurring in almost one-third of the participants (31.85 %). This result is comparable with studies done in India and Vietnam, occurring in 34.42 % and 38.5 % of the patients, respectively [10,31]. However, our result is lower than previous studies done in Ethiopia (70 %) and China (65.4 %), but higher than a study done in South Korea (18.4 %) [19,32,33]. The variation between the results could be due to the difference in the minimum follow-up time, GI disturbance definition, type, and profession of health workers giving care at clinics, monitoring, and follow-up mechanisms of treatment centers. Subgroup disturbances in our study included nausea and vomiting (27.74 %), abdominal pain (1.03 %), and epigastric pain (5.48 %). Nausea and vomiting were severe enough to cause serious adverse events in 2.74 % % of the patients, while 2.05 % had regimen modifications.

Peripheral neuropathy occurred in 21.92 % of the patients, which is much higher than a study in Ethiopia, which was seen in 9.14 % of the patients, but the regimen in this study didn't include new and repurposed second line drugs such as Lzd, which could have contributed to the lower rate of peripheral neuropathy [16]. Furthermore, temporary and permanent drug discontinuation occurred in 4.1 % and 6.5 % of the patients, respectively. Arthralgia was the 3rd most common ADR, occurring in 17.47 % of the patients, comparable with a study done in India (14.38 %) [34]. However, it is lower than reported in china (67.5 %) [25,32].

Visual disturbances occurred in 16.44 % of the patients, resulting in temporary and permanent drug discontinuation in 6.5 % and 8.22 %, respectively. This result is consistent with a study done in western India in which visual changes occurred in 16 % of the patients [35].

Psychiatric disturbances were found in 8.22 % of the patients, in line with studies done in Indonesia (7.5 %) and China (9.28 %) [36,37]. However, it is lower than a 2019 study done in Ethiopia (15.32 %) and Vietnam (33.75 %) [10,16]. This can be due to differences in the definition of psychiatric disorders and discrepancies between studies on the number of patients on Cs-containing regimens. The most common psychiatric disorder in our study was insomnia (4.45 %), followed by hallucinations (3.08 %), depression (1.37 %), and suicidal attempts in 2 patients (0.68 %). Hallucinations caused serious adverse event in 3 patients.

In this study, hematologic abnormalities such as anemia and myelosuppression occurred in 4.79 % and 0.34 % of the patients,

Table 4
Characteristics and implication of ADRs during DR-TB treatment in public hospitals in Addis Ababa, Ethiopia from 2017 to 2023. (N = 292).

ADR	N (%)	Month of presentation (median in month)	Temporary drug discontinuation N (%)	Permanent drug discontinuation N (%)	RM N (%)	DR N (%)	SAE N (%)
GI disturbance	93 (31.85)						
Nausea and vomiting	81 (27.74)	3	1(0.34)	0	6(2.05)	0	8(2.74)
Epigastric pain	16(5.48)	4	0	0	0	0	0
Abdominal pain	3(1.03)	3	0	0	0	0	0
Peripheral neuropathy	64 (21.92)	10	12(4.1)	19(6.5)	0	5(1.71)	0
Arthralgia	51 (17.47)	6	6(2.05)	6(2.05)	0	3(1.02)	0
Visual disturbance	48 (16.44)	7.5	19(6.5)	24(8.22)	0	0	0
Psychiatric disturbances	24(8.22)						
Hallucination	9 (3.08)	3	4(1.37)	2(0.68)	0	2(0.68)	3(1.02)
Depression	4 (1.37)	5.5	1(0.34)	0	0	1(0.34)	0
Insomnia	13 (4.45)	6	1(0.34)	2(0.68)(	0	0	0
Suicidal attempts	2 (0.68)	9.5	0	2(0.68)	0	0	0
Anemia	14(4.79)	7	5(1.71)	5(1.71)	0	3(1.02)	12 (4.1)
Hearing loss	10(3.42)	3	0	8(2.73)	0	0	3(1.02)
Hepatotoxicity	9(3.08)	2	6(2.05)	1(0.34)	1(0.34)	0	6(2.05)
Prolonged QT interval	5(1.71)	3	1(0.34)	2(0.68)	0	1(0.34)	0
Reaction at injection site	2(0.68)	3.5	0	0	0	0	0
Nephrotoxicity	2(0.68)	2	0	2(0.68)	0	0	1(0.34)
Hypothyroidism	1(0.34)	6	0	0	0	0	0
Myelosuppresion	1(0.34)	7	0	1(0.34)	0	0	1(0.34)

Abbreviations; RM: Regimen modification, SAE: Serious adverse event, DR: Dose reduction

respectively, but were serious adverse drug reactions resulting in life-threatening conditions and prolonged hospitalization. Prolonged Lzd use has been associated with hematologic abnormalities, but it is highly dependent on the dose, duration of use, and is reversible with appropriate treatment.

Hearing loss occurred in 3.42 % of the patients, and 1.02 % had serious adverse events that resulted in permanent disability. The prevalence of ototoxicity was higher in studies in Italy (11.5%), and Pakistan (11.2 %) (13, 14, 38). This can be due to the routine use of injectable aminoglycosides in the above studies, and the absence of routine audiometric evaluation during treatment in the Ethiopian context could have contributed to the lower rate of ADRs.

Additionally, 3.08 % of the patients had hepatotoxicity comparable with studies done in Vietnam (5.8 %) and India (1.6 %) [10,31]. A prolonged QT interval was seen in 5 (1.71 %) of the patients. This result is much lower than a study in Ethiopia (16.7 %), which showed preliminary results primarily focusing on patients only on Bdq and Dlm-containing regimens (19). Nephrotoxicity occurred in 2 (0.68 %) patients on whom the drug was permanently discontinued and the other needed prolonged hospitalization. This result is much lower than another study done in Ethiopia, in which nephrotoxicity was found in 6.7 % of the patients, but this study predominantly included patients who are on aminoglycoside-containing regimens, which could have contributed to the higher prevalence of nephrotoxicity [22].

In the multivariable regression, age, anemia, and patient admission or hospitalization were factors associated with ADRs. ADRs occurred more frequently in the older age groups of 25–49 and $\geq$ 50. This result is in line with studies done in Ethiopia, Iran, and Pakistan [15,16,38]. As age increases, there are changes in drug pharmacokinetics and pharmacodynamics resulting in an alteration in the hepatic blood flow distribution, and combined with a reduced renal function, the clearance rate of metabolized drugs is reduced. Additionally, since the older age groups have a higher prevalence of chronic diseases, they are more likely to take multiple drugs simultaneously, increasing the risk of ADRs [39,40].

Anemia is another factor associated with ADRs in DR-TB patients. Anemic patients at presentation were 58 % more likely to develop ADRs compared to non-anemic ones. This is in line with studies done in Ethiopia and Peru [16,41]. Anemia is one of the most common laboratory abnormalities present in TB, occurring due to nutritional deficiency, malabsorption and chronic inflammation [42]. Furthermore, other studies have also shown that the presence of anemia shows severity of the disease, with the potential to affect subsequent treatment outcomes and increase the risk of recurrent TB infection [43]. On the other hand, many of the medications such as H, Cs, E, Z, Cfz, Lfx, and Lzd used for DR-TB can also cause hematologic ADRs, including anemia [44].

Patient admission status or hospitalization is another factor associated with the occurrence of ADR. Admitted patients were 53 % more likely to develop events compared to those on ambulatory care. Since MDR-TB patients could be effectively treated in an ambulatory basis, a clinic–based ambulatory mode is the main model of care, and hospitalization is reserved for patients with severe medical or social justification. Admitted patients usually have a more severe disease and are more at risk for a greater number of ADRs [18]. Additionally, hospitalized patients usually receive close and frequent follow-up during treatment, which can lead to increased reporting of ADRs among both health care professionals and patients.

Although this study tried to show the occurrence of ADRs after the introduction of new and repurposed drugs, there are a few limitations. Since it is a retrospective study based on a review of the patient charts, the collected data solely depends on available recordings of the patient charts, which can lead to an underestimation of reported ADRs. The retrospective nature has also made it difficult to establish a causal relationship. Additionally, ADRs such as hearing loss and visual disturbance were not routinely assessed using objective methods and were dependent on the clinical presentation for diagnosis due to limited resources.

Table 5
Bivariate and Multivariate analysis of factors associated with occurrence of adverse drug reactions during DR-TB treatment in public hospitals in Addis Ababa, Ethiopia, from 2017 to 2023. (N = 292).

Variables	Event n = 186 (%)	Censored n = 106 (%)	CHR (95 % CI)	AHR (95 % CI)	P value
Age					
1—24	39(21)	44(41.5)	1	1	
25–49	103 (55.3)	54(50.9)	1.49 (1.03,2.16)	1.53 (1.05,2.21)	0.023*
≥50	44 (23.7)	8(7.5)	2.20 (1.43,3.40)	1.87 (1.19,2.93)	0.006*
HIV status					
Negative	134(72)	91(85.8)	1	1	
Positive	52(28)	15(14.2)	1.47(1.06, 2.03)	1.12 (0.79,1.58)	0.506
Registration group					
New	87 (46.8)	45(42.4)	1	1	
Relapse	73 (39.2)	36(34)	1.04(0.76, 1.43)	0.98(0.71, 1.34)	0.909
Treatment after failure or LTFU	26(14)	25(23.6)	0.64(0.41, 0.99)	0.64(0.41, 0.99)	0.049
Concomitant medication use					
No	119(64)	85(80.2)	1	1	
Yes	67(36)	21(19.8)	1.45 (1.08,1.97)	0.96 (0.63,1.47)	0.866
Treatment regimen					
Short term regimen	40 (21.5)	48(45.3)	1	1	
Long term regimen	23 (12.4)	8(7.5)	1.38 (0.82,2.32)	1.26 (0.75,2.13)	0.374
Long term regimen with new drug	123 (66.1)	50(47.2)	1.34 (0.93,1.93)	1.09 (0.75,1.60)	0.624
Patient admission					
No	131 (70.4)	91(85.8)	1	1	
Yes	55 (29.6)	15(14.2)	1.64 (1.20,2.26)	1.53 (1.10,2.13)	0.011*
Anemia					
No	126 (67.7)	95(89.6)	1	1	
Yes	60 (32.3)	11(10.4)	1.65 (1.21,2.25)	1.58 (1.16,2.17)	0.004*

AHR: Adjusted hazard ratio CI: Confidence interval.
Short term regimens Km-Mfx-Pto-Cfz-Z-HH-E or Bdq-Lfx-Cfz-Z-E Hh-Eto.
Long term regimen with new drug Bdq-Lfx/Mfx-Lzd-Cfz-Cs or Bdq-Lfx/Mfx-Lzd-Cfz-Cs-Dld.
Long term regimen Lfx-Cm-Pto/Eto-Cs-Z.

5. Conclusion

More than half of the participants had experienced at least one ADR. The incidence of ADR was 8.10 per 100 person-month observation. Age between 25–49, age greater than or equal to 50 years, patient admission, and baseline anemia were all independent predictors of ADRs during MDR TB treatment. GI disturbance, followed by peripheral neuropathy and arthralgia, were the most commonly occurring ADRs during treatment. Additionally, nausea and vomiting, anemia, and hepatotoxicity were the most commonly reported ADRs that caused a serious adverse event. Lastly, 76.03 % of the patients had a good treatment outcome, while 19.52 % had poor treatment outcomes. Special attention should be given to susceptible groups of older age, hospitalized patients, and anemic patients on baseline for early prediction, timely management, and appropriate formulation of treatment regimens to address ADRs. Additionally, a prospective multicenter study with a larger sample size is recommended to increase the generalizability of findings. Future studies should also further explore the long-term squeal of ADRs.

6. Ethics declarations

Ethics approval and consent to participate.

Investigator obtained ethical approval from the Scientific and Ethics Review Committee of the Center for Innovative Drug Development and Therapeutic Trials for Africa (CDT-Africa), College of Health Sciences, Addis Ababa University. A waiver of informed consent was requested. Ethical clearance and support letters were obtained from St. Peter Specialized Hospital and ALERT Hospital. Confidentiality was maintained strictly.

CRediT authorship contribution statement

Bisrat Solomon: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Yimtubezinash Woldeamanuel:** Writing – review & editing, Supervision, Data curation. **Tigest Ajeme:** Writing – review & editing, Supervision, Data curation. **Mbazi Senkoro:** Writing – review & editing, Supervision, Data curation. **Tsegahun Manyazewal:** Writing – review & editing, Supervision, Data curation.

Funding

This study was produced by EACCR3, which is part of the EDCTP2 programme supported by the European Union (grant number CSA2020NoE-3102-EACCR3). The views and opinions of the authors expressed herein do not necessarily state or reflect those of EDCTP.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors thank the Center for Innovative Drug Development and Therapeutic Trials for Africa (CDT-Africa), College of Health Sciences, Addis Ababa University, Ethiopia, for providing technical support and managing the grant.

References

[1] Tuberculosis2024.
[2] Global tuberculosis report 2024. Geneva: World Health Organization; 2024. Licence: CC BY-NC-SA 3.0 IGO.
[3] Tuberculosis in the WHO African Region: 2023 progress update. Brazzaville: WHO African Region, 2023. Licence: CC BY-NC-SA 3.0 IGO.
[4] Khan S, Silsarma A, Mahajan R, Khan S, Davuluri P, Sutar N, et al. Treatment outcomes among patients with isoniazid mono-resistant tuberculosis in Mumbai, India: a retrospective cohort study. Journal of Clinical Tuberculosis and Other Mycobacterial Diseases 2024;37:100481.
[5] Gupta A, Kumar V, Natarajan S, Singla R. Adverse drug reactions & drug interactions in MDR-TB patients. Indian J Tuberc 2020;67(4s):S69–78.
[6] Briefing Note Safety of medicines -adverse drug reactions Key facts WHO.
[7] Prasad R, Singh A, Gupta N. Adverse drug reactions in tuberculosis and management. Indian J Tuberc 2019;66(4):520–32.
[8] Ahmad N, Javaid A, Syed Sulaiman SA, Afridi AK, Zainab KAH. Occurrence, management, and risk factors for adverse drug reactions in multidrug resistant tuberculosis patients. Am J Ther 2018;25(5):e533–40.
[9] Aznar ML, Rando Segura A, Moreno MM, Espasa M, Sulleiro E, Bocanegra C, et al. Treatment outcomes and adverse events from a standardized multidrug-resistant tuberculosis regimen in a rural setting in angola. Am J Trop Med Hyg 2019;101(3):502–9.
[10] Ngoc NB, Vu Dinh H, Thuy NT, Quang DV, Huyen CTT, Hoa NM, et al. Active surveillance for adverse events in patients on longer treatment regimens for multidrug-resistant tuberculosis in Viet Nam. PLoS One 2021;16(9):e0255357.
[11] Achalu DL, Mohammed FG, Teferi M. Magnitude and impacts of adverse events of injectable containing shorter regimen in programmatic management of multi-drug resistant tuberculosis in ethiopia: a retrospective cohort study. Ther Clin Risk Manag 2023;19:889–901.
[12] El-Din MAT HH, El-Tantawy AM. Adverse reactions among patients being treated for multi-drug resistant tuberculosis in Egypt from July 2006 to January 2009.

Egyptian Journal of Chest Diseases and Tuberculosis 2015 Jul;64(3):657–64. 38. 2015.
[13] Ategyeka PM, Muhoozi M, Naturinda R, Kageni P, Namugenyi C, Kasolo A, et al. Prevalence and factors associated with reported adverse-events among patients on multi-drug-resistant tuberculosis treatment in two referral hospitals in Uganda. BMC Infect Dis 2023;23(1):149.
[14] Gualano G, Mencarini P, Musso M, Mosti S, Santangelo L, Murachelli S, et al. Putting in harm to cure: drug related adverse events do not affect outcome of patients receiving treatment for multidrug-resistant Tuberculosis. experience from a tertiary hospital in Italy. PLoS One 2019;14(2):e0212948.
[15] Farazi A, Sofian M, Jabbariasl M, Keshavarz S. Adverse reactions to antituberculosis drugs in iranian tuberculosis patients. Tuberculosis Research and Treatment 2014;2014:412893.
[16] Merid MW, Gezie LD, Kassa GM, Muluneh AG, Akalu TY, Yenit MK. Incidence and predictors of major adverse drug events among drug-resistant tuberculosis patients on second-line anti-tuberculosis treatment in Amhara regional state public hospitals; Ethiopia: a retrospective cohort study. BMC Infect Dis 2019;19(1):286.
[17] Bogale L, Tenaw D, Tsegaye T, Abdulkadir M, Akalu TY. A score to predict the risk of major adverse drug reactions among multi-drug resistant tuberculosis patients in Southern Ethiopia, 2014-2019. Infect Drug Resist 2022;15:2055–65.
[18] Guidelines for Clinical and Programmatic Management of TB, TB/HIV, DR-TB and Leprosy in Ethiopia . 7th ed. 2021. Ethiopia2021 2021.
[19] Tesema E, Wares F, Bedru A, Negeri C, Molla Y, Gemechu D, et al. Experiences of introducing new drugs for drug-resistant TB at the ALERT Hospital, Addis Ababa, Ethiopia, 2017-2019. Public Health Action 2021;11(2):50–2.
[20] Bezu H, Seifu D, Yimer G, Mebrhatu T. Prevalence and risk factors of adverse drug reactions associated multidrug resistant tuberculosis treatments in selected treatment centers in Addis Ababa Ethiopia. Journal of Tuberculosis Research 2014; 2014:144–54.
[21] Wondwossen A, Waqtola C, Gemeda A. Incidence of antituberculosis-drug-induced hepatotoxicity and associated risk factors among tuberculosis patients in Dawro Zone, South Ethiopia: a cohort study. Int J Mycobacteriol 2016;5(1):14–20.
[22] Shibeshi W, Sheth AN, Admasu A, Berha AB, Negash Z, Yimer G. Nephrotoxicity and ototoxic symptoms of injectable second-line anti-tubercular drugs among patients treated for MDR-TB in Ethiopia: a retrospective cohort study. BMC Pharmacol Toxicol 2019;20(1):31.
[23] Aradimitriou N., Cheru F., Wondimu A., Yacobi H., Eyob AE., Belay F., Temesgen T. K., Eyana SM., Yoseph S. (2021) 'The State of Addis Ababa 2021: Towards A Healthier City'. Addis Ababa: UN Habitat.
[24] Guideline on haemoglobin cutoffs to define anaemia in individuals and populations. Geneva: World Health Organization; 2024. Licence: CC BY-NC-SA 3.0 IGO.
[25] Massud A, Syed Sulaiman SA, Ahmad N, Shafqat M, Chiau Ming L, Khan AH. Frequency and management of adverse drug reactions among drug-resistant tuberculosis patients: analysis from a prospective study. Front Pharmacol 2022;13: 883483.
[26] Weir CB, Jan A. BMI Classification Percentile And Cut Off Points. [Updated 2023 Jun 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/sites/books/NBK541070/.
[27] Linh NN, Viney K, Gegia M, Falzon D, Glaziou P, Floyd K, et al. World Health Organization treatment outcome definitions for tuberculosis: 2021 update. Eur Respir J 2021;58(2).
[28] WHO consolidated guidelines on tuberculosis: Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update [Internet]. Geneva: World Health Organization; 2022. Definitions. Available from: https://www.ncbi.nlm.nih.gov/books/NBK588561/.
[29] Nasasira M, Kalyango JN, Mupere E, Baluku JB. Incidence and predictors of adverse drug events among people receiving drug resistant tuberculosis treatment in uganda: 8-year retrospective cohort study. Ther Clin Risk Manag 2022;18: 1117–27.
[30] Buziashvili M, Davtyan H, Sereda Y, Denisiuk O, Gozalov O, Lomtadze N, et al. Incidence rate and time to serious adverse events among rifampicin resistant tuberculosis patients in Georgia treated with new and repurposed anti-tuberculosis drugs, 2016-2018. Monaldi Arch Chest Dis. 2021;91(1).
[31] Piparva KG, Jansari G, Singh AP. Evaluation of treatment outcome and adverse drug reaction of directly observed treatment (DOT) plus regimen in multidrug-resistant tuberculosis (MDR-TB) patients at district tuberculosis centre Rajkot. Perspect Clin Res 2018;9(4):165–9.
[32] Zhang Y, Wu S, Xia Y, Wang N, Zhou L, Wang J, et al. Adverse events associated with treatment of multidrug-resistant tuberculosis in china: an ambispective cohort study. Med Sci Monit 2017;23:2348–56.
[33] Yang TW, Park HO, Jang HN, Yang JH, Kim SH, Moon SH, et al. Side effects associated with the treatment of multidrug-resistant tuberculosis at a tuberculosis referral hospital in South Korea: a retrospective study. Medicine (Baltimore) 2017; 96(28):e7482.
[34] Dela AI, Tank NKD, Singh AP, Piparva KG. Adverse drug reactions and treatment outcome analysis of DOTS-plus therapy of MDR-TB patients at district tuberculosis centre: a four year retrospective study. Lung India 2017;34(6):522–6.
[35] Rupani MP, Dave JD, Parmar VB, Singh MP, Parikh KD. Adverse drug reactions and risk factors for discontinuation of multidrug-resistant tuberculosis regimens in Gujarat, western India. Natl Med J India 2020;33(1):10–4.
[36] Nilamsari WP, Rizqi MF, Regina NO, Wulaningrum PA, Fatmawati U. Adverse drug reaction and its management in tuberculosis patients with multidrug resistance: a retrospective study. J Basic Clin Physiol Pharmacol 2021;32(4):783–7.
[37] Pang Y, Liu R, Song Y, Lv Z, Gao M, Nie L, et al. High incidence of psychiatric disorders associated with cycloserine treatment of multidrug-resistant tuberculosis patients: a cohort study in Beijing China. Infect Drug Resist 2022;15:3725–32.
[38] Khan FU, Khan A, Khan FU, Hayat K, Rehman AU, Chang J, et al. Assessment of adverse drug events, their risk factors, and management among patients treated for multidrug-resistant TB: a prospective cohort study from Pakistan. Front Pharmacol 2022;13:876955.
[39] Woo S-D, Yoon J, Doo G-E, Park Y, Lee Y, Lee S-H, et al. Common causes and characteristics of adverse drug reactions in older adults: a retrospective study. BMC Pharmacol Toxicol 2020;21(1):87.
[40] Petrovic M, van der Cammen T, Onder G. Adverse drug reactions in older people: detection and prevention. Drugs Aging 2012;29(6):453–62.
[41] Chung-Delgado K, Revilla-Montag A, Guillen-Bravo S, Velez-Segovia E, Soria-Montoya A, Nuñez-Garbin A, et al. Factors associated with anti-tuberculosis medication adverse effects: a case-control study in Lima, Peru. PLoS One 2011;6 (11):e27610.
[42] Dasaradhan T, Koneti J, Kalluru R, Gadde S, Cherukuri SP, Chikatimalla R. Tuberculosis-associated anemia: a narrative review. Cureus 2022;14(8):e27746.
[43] de Mendonça EB, Schmaltz CA, Sant'Anna FM, Vizzoni AG, Mendes-de-Almeida DP, de Oliveira RVC, et al. Anemia in tuberculosis cases: a biomarker of severity? PLoS One 2021;16(2):e0245458.
[44] Minardi ML, Fato I, Di Gennaro F, Mosti S, Mastrobattista A, Cerva C, et al. Common and rare hematological manifestations and adverse drug events during treatment of active TB: a state of art. Microorganisms 2021;9(7).