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Adverse drug reactions of first-line antitubercular drugs: A retrospective study on characteristics, management, factors, and impacts

Ai Ling Oh[1,2], Mohd Makmor-Bakry[1,3]✉, Farida Islahudin[1], Chuo Yew Ting[4], Swee Kim Chan[5], Siew Teck Tie[5]

[1]*Centre of Quality Management of Medicines, Faculty of Pharmacy, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia*

[2]*Department of Pharmacy, Sarawak General Hospital, Ministry of Health Malaysia, Kuching, Sarawak, Malaysia*

[3]*Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia*

[4]*Department of Sarawak State Health, Ministry of Health Malaysia, Kuching, Sarawak, Malaysia*

[5]*Division of Respiratory Medicine, Department of Internal Medicine, Sarawak General Hospital, Ministry of Health Malaysia, Kuching, Sarawak, Malaysia*

ABSTRACT

Objective: To elucidate the characteristics, management strategies, risk factors, and clinical impacts associated with adverse drug reactions (ADRs) induced by first-line antitubercular drugs to enhance tuberculosis (TB) management.

Methods: A retrospective cohort study was conducted by retrieving drug-susceptible TB records among adult patients who received TB treatment from 2018 to 2021 at 10 public health clinics in Sarawak, Malaysia. Only the initial TB treatment and occurrence of specific ADRs within the study period were considered. Regression analysis was performed to identify the risk factors associated with both overall ADRs and individual types of ADRs.

Results: Among 2 953 cases, 705 (23.9%) developed ADRs. Cutaneous reactions were the most prevalent (47.1%), followed by hepatotoxicity (32.8%) and gastrointestinal disturbances (29.8%). Six out of seven types of ADRs investigated occurred within the intensive phase, mostly manifesting at approximately 2 weeks of initiation. Hepatotoxicity resulted in the majority (85.3%) of treatment discontinuations, while vision problems led to treatment modifications in half of the cases. Risk factors for all ADRs included age ≥60 years, females, illicit drug use, and comorbidities such as HIV-positive, diabetes, and chronic liver disease. Alcohol consumption was independently associated with hepatotoxicity. ADRs caused around one-third of interruptions exceeding 2 weeks (33.0%) and subsequently necessitated treatment restarts (34.5%).

Conclusions: Understanding these various aspects contributes to improving the overall management of ADRs in TB treatment. Close ADR monitoring and reporting are essential to strengthen ADR management.

KEYWORDS: Adverse events; Cutaneous reactions; Hepatotoxicity; Gastrointestinal disturbances; Risk factors; Tuberculosis

1. Introduction

Tuberculosis (TB) is an ancient infectious illness discovered over a century ago that continues to be a global epidemic, predominantly

Significance

This study evaluated the characteristics, risk factors, management, and impacts of adverse drug reactions (ADRs) associated with first-line antitubercular drugs. ADRs commonly occurred during the intensive phase, manifesting as cutaneous reactions, hepatotoxicity, and gastrointestinal disturbances. Older age, female sex, illicit drug use, and comorbidities such as HIV infection, diabetes, and chronic liver disease were associated with a higher risk of experiencing ADRs. These reactions often led to treatment interruption, modification, restart, and hospitalization. The findings highlighted the importance of vigilant ADR monitoring, particularly for high-risk groups, to enable early detection and timely management.

✉To whom correspondence may be addressed. E-mail: mohdclinpharm@ukm.edu.my

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endemic in low- and middle-income countries in Asia and Africa[1,2]. Globally, an estimated 10.6 million new cases were reported, with an incidence rate of 133 cases per 100 000 population in 2022[2]. Approximately 1.3 million TB-related deaths have been reported, ranking TB as the 13th leading cause of death[2]. It commonly affects the lungs even though many other organs can be involved. The bacterium can remain dormant and undetected for many years until its reactivation leads to TB disease, causing widespread disease transmission[3]. This poses challenges for TB control and prevention despite advancements in diagnostics and treatment modalities. Pharmacological intervention is the mainstay management for TB. Treatment of drug-susceptible TB consists of four first-line antitubercular drugs, namely isoniazid, rifampicin, ethambutol, and pyrazinamide, with the first two drugs serving as the backbone over a treatment period lasting at least 6 months[4]. The use of a four-drug combination in treating TB infection is highly effective, with approximately 85% achieving a successful treatment outcome[5]. However, this combination commonly leads to adverse drug reactions (ADRs) in up to 85% of cases, manifesting in a wide spectrum, including cutaneous reactions, gastrointestinal disturbances, hepatotoxicity, arthralgia, and peripheral neuropathy, among others[6]. The management of ADRs can be symptomatic in mild presentations, but in certain moderate to severe conditions, treatment modification and discontinuation are inevitable[6]. In meta-analyses conducted among Asian and African populations, ADRs of antitubercular drugs doubled the risk of treatment interruption or non-adherence[7,8]. Apart from the fear of unbearable adverse events among patients, potential inappropriate management of ADRs could lead to TB treatment interruption[6,8].

Malaysia bears an intermediate TB burden, ranging between 91 to 97 cases per 100 000 population from 2018 to 2021[9]. However, Sarawak State, Malaysia, on Borneo Island, suffers a high TB burden, ranging between 104 to 108 cases per 100 000 population from 2018 to 2020, with a reduction of case detection to 89 cases per 100 000 population in the post-COVID era in 2021[10]. Approximately 8.5 times the risk of treatment interruption secondary to ADRs of antitubercular drugs has also been reported[11,12]. Given the high burden of TB and the substantial risk of treatment interruption due to ADRs from antitubercular drugs, this study aimed to assess the characteristics, management, risk factors, and impacts associated with ADRs of antitubercular drugs.

2. Subjects and methods

2.1. Study design and population

A retrospective cohort study was initially conducted between March 2022 to January 2023, investigating predictive factors for treatment interruption among 2 953 drug-susceptible TB patients diagnosed between 2018 to 2021 at 10 public health clinics in Sarawak State, Malaysia[12]. Given the high risk of treatment interruption due to ADRs observed in the initial study, the present study undertook a comprehensive analysis of various aspects of ADRs associated with antitubercular drugs, utilizing data collected concurrently from the same sampling frame.

2.2. Inclusion and exclusion criteria

This study involved adult TB patients aged ≥18 years who were diagnosed with drug-susceptible TB. Patients were treated with four first-line antitubercular drugs: isoniazid, rifampicin, ethambutol, and pyrazinamide. Standard weight-based dosing as per the national clinical practice guideline was employed, with an average dose of 5 mg/kg, 10 mg/kg, 15 mg/kg, and 25 mg/kg, respectively, administered once daily. However, ethambutol and pyrazinamide were adjusted to three times weekly dosing for those with creatinine clearance below 30 mL/min[13]. In addition to individual antitubercular drugs, a fixed-dose combination was also provided according to the standard weight-based dosing guideline[13]. As patients could have undergone multiple TB treatment courses between 2018 to 2021, only the initial treatment was considered to prevent data duplication. Similarly, in cases where ADRs of the same category occurred more than once during the treatment course, only the initial instance was considered.

Exclusion criteria encompassed incomplete documentation regarding medication administration, treatment process, or outcomes. Due to substantial missing data associated with treatment outcomes categorized as ‘death’ and ‘transfer-out’, such cases were generally excluded.

2.3. Data collection

Data retrieval involved reviewing paper-based TB records for each patient at the clinics. A standardized data collection form was used to gather all information. This encompassed demographic characteristics (age and sex), lifestyle factors (smoking, alcohol intake, and illicit drug use), comorbidities, disease and treatment-relevant data [TB site, TB medications (types, changes, and restarting treatment)], interruption days, ADRs (characteristics and management strategies), hospitalization, and treatment outcomes.

The characteristics of ADRs such as the types, onset, and respective interruption days were recorded. The management of ADRs was assessed throughout their occurrence, with the eventual approach recorded and categorized as either stopping, modifying, or continuing treatment. Stopping refers to the discontinuation of treatment or suspected drugs with the remainder deemed inadequate to form an effective regimen, leading to treatment interruption. Treatment modification involves changes in drugs without interruptions or compromising the effectiveness of the treatment regimen. Continuing treatment entails maintaining antitubercular drugs without treatment interruption.

Factors identified as potential contributors to ADRs were predetermined as a priori in the analysis. This included demographic characteristics such as age and sex, unhealthy lifestyles (*e.g.* smoking, alcohol intake, and illicit drug use), and comorbidities such as human immunodeficiency virus (HIV) status, diabetes, chronic renal failure (creatinine clearance <30 mL/min), and chronic liver problems (*e.g.* hepatitis and liver cirrhosis).

The clinical impacts of ADRs were assessed, considering the duration of treatment interruption, hospitalization, changes in medications, treatment restart, and the final classification as per the World Health Organization's (WHO) TB treatment outcome assessment, indicating loss to follow-up, failure, or success (cure or completed)[14].

2.4. Sample size

This study utilized the same sampling frame from the initial cohort study, which had a sample size of 2953[12]. The ADR prevalence in the present cohort was 23.9% and nine factors were included in the risk factors regression analysis. Thus, the initial 2953 samples were found to be sufficient for the present study, meeting the minimum sample size requirement of 377 based on the ADR prevalence and including factors, calculated according to the formula by Peduzzi *et al*[15].

2.5. Data analysis

Data analysis was performed using the SPSS statistical software version 22.0 (IBM. Armonk, New York, USA). Descriptive statistics were utilized to summarize the data regarding ADR characteristics, management strategies, and clinical impacts using median (interquartile range, IQR), frequency, and percentage where appropriate. Differences among variables for population characteristics and clinical impacts were analyzed using the *Chi*-square test. Multiple logistic regression was employed to identify factors associated with ADRs. Initially, all nine variables were included in both Forward LR and Backward LR selection methods. Variables that remained in the final steps were further analyzed using the Enter method, with checks for multicollinearity and interaction terms, to determine the final model. Statistical significance was set at $P<0.05$.

2.6. Research ethics and patient consent

This research was registered with the National Medical Research Register bearing the Registration Number NMRR ID-21-01961-PHS with the ethical approval granted by the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia. The research ethics approval was also obtained from Universiti Kebangsaan Malaysia (UKM) Research Ethics Committee (JEP-2022-502). Patient consent was not required due to the retrospective cohort study design.

3. Results

Among 2953 patients with drug-susceptible TB, the majority were male (65.9%) and under 60 years old (71.0%). Approximately three-quarters of the population were non- or ex-smokers and non-diabetics. Over 90% were non- or ex-alcoholics, non-illicit drug users, HIV-negative, and without chronic kidney or liver disease. Pulmonary TB comprised the majority of cases (77.1%), and the vast majority (91.8%) were treated with a fixed-drug combination (Table 1).

3.1. Characteristics of adverse drug reactions

Approximately one-quarter (23.9%, n=705) of patients experienced ADRs secondary to first-line antitubercular drugs. Seven types of commonly reported ADRs included cutaneous reactions, hepatotoxicity, gastrointestinal disturbances, musculoskeletal problems, neurotoxicity, vision problems, and ototoxicity. Among those with ADRs, nearly half (47.1%) experienced cutaneous reactions, while around one-third suffered from hepatotoxicity (32.8%) and gastrointestinal disturbances (29.8%), with the remaining ADRs occurring in less than 10% of cases. The onset of ADRs was mostly observed at approximately 2 weeks of treatment for cutaneous reactions, hepatotoxicity, gastrointestinal disturbances, and vision problems. Other reactions such as musculoskeletal problems were observed at approximately 1 month, and ototoxicity and neurotoxicity were reported at around 2 months or beyond. (Figure 1).

3.2. Management of adverse drug reactions

The approach to managing these ADRs varied depending on their severity as determined by clinical judgment (Figure 2). More than half of the patients with cutaneous reactions (55.1%), gastrointestinal disturbances (52.4%), and musculoskeletal problems (56.9%), and around three-quarters (73.5%) of those with neurotoxicity continued their TB medications while receiving symptomatic treatment. For example, patients with cutaneous reactions were treated with antihistamines and topical preparations such as aqueous cream to alleviate skin rash, dryness, and itchiness. Those with gastrointestinal discomfort received antacids or acid suppressant drugs and antiemetics or prokinetics for those who experienced nausea and vomiting. Some were also advised to take antitubercular drugs post-meals to reduce gastrointestinal disturbances. For musculoskeletal problems, analgesics such as paracetamol, NSAIDs, and topical agents were used to reduce joint or muscle pain. Mild neurotoxicity cases such as those with peripheral numbness were generally

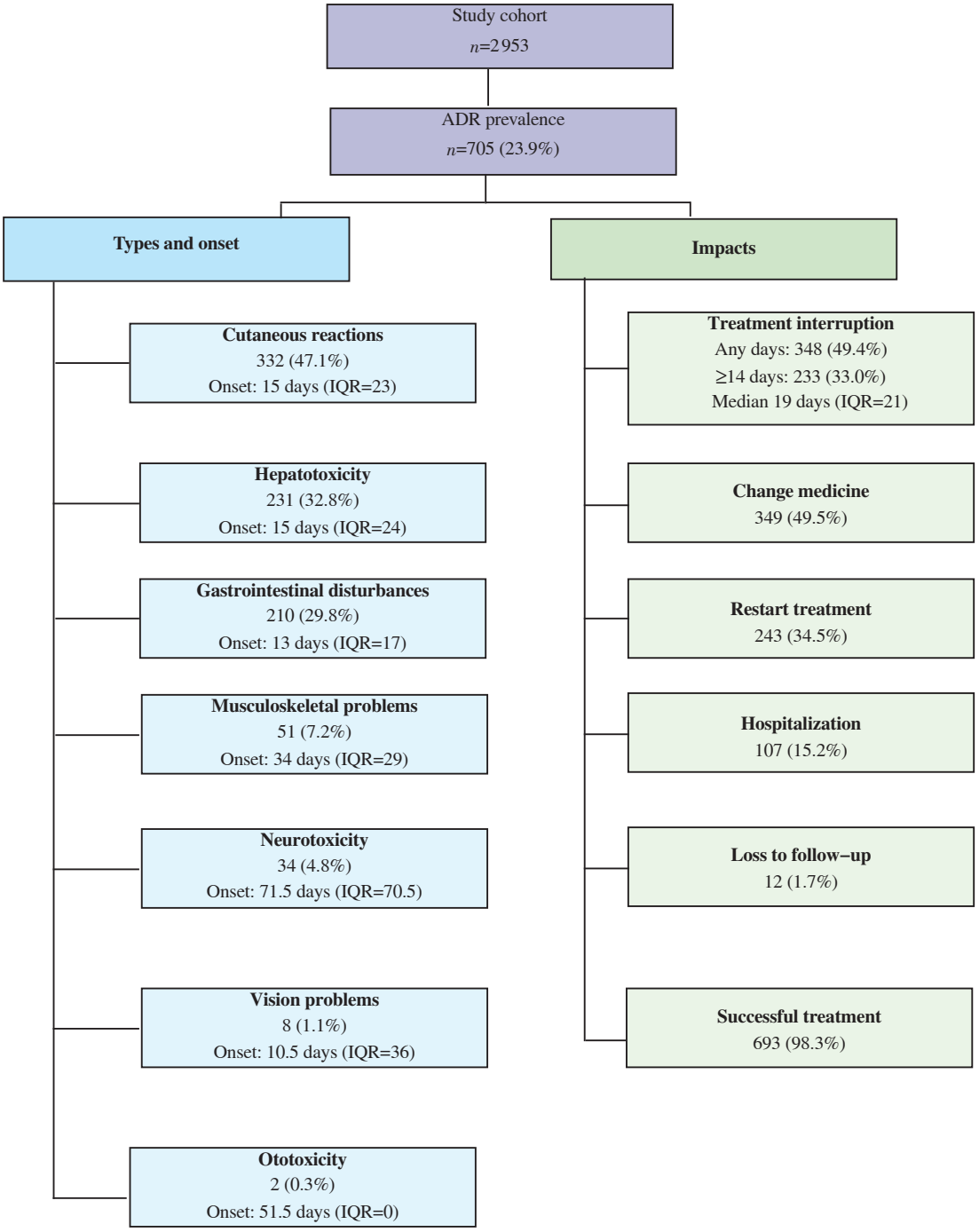

Figure 1. Characteristics and impacts of adverse drug reactions (ADRs). IQR: interquartile range.

managed by increasing the dose of Vitamin B6 supplementation.

The majority (85.3%) of hepatotoxicity cases were managed by discontinuing antitubercular drugs for alanine transaminase (ALT) raised beyond 5 times or symptomatic presentations with ALT beyond 3 times the upper limit of normal, as three out of four antitubercular drugs have the potential to cause liver injury. Treatment discontinuations were also observed in about 36%-38% of patients who experienced cutaneous reactions, gastrointestinal disturbances, and vision problems.

Modifications of TB regimens were observed in half of the patients who experienced visual disturbances. In some ADR cases, replacement of the suspected offending drugs with ofloxacin and/or streptomycin was also practiced to avoid any treatment interruptions. Switching a fixed-dose combination to individual TB medications was also attempted in many cases in managing ADRs.

3.3. Factors associated with adverse drug reactions

The associated factors of ADRs were evaluated for all ADR cases, and individually for the three most prevalent ADRs in this cohort (Table 2). Aged 60 years and above consistently demonstrated a higher risk of ADRs, ranging from approximately 1.5 to 1.7 times the odds across all and individual ADRs. Male sex was

Table 1. Characteristics of the study population (n=2953).

Characteristics	Total	No ADR	ADR	P value
Age, years (n=2953)				
<60	2097 (71.0)	1653 (78.8)	444 (21.2)	<0.001
≥60	856 (29.0)	595 (69.5)	261 (30.5)	
Sex (n=2953)				
Male	1947 (65.9)	1511 (77.6)	436 (22.4)	0.009
Female	1006 (34.1)	737 (73.3)	269 (26.7)	
Smoking (n=2953)				
Yes	734 (24.9)	585 (79.7)	149 (20.3)	0.009
No/Ex-smoker	2219 (75.1)	1663 (74.9)	556 (25.1)	
Alcohol intake (n=2951)				
Yes	185 (6.3)	136 (73.5)	49 (26.5)	0.392
No/Ex-alcoholic	2766 (93.7)	2110 (76.3)	656 (23.7)	
Illicit drug use (n=2953)				
Yes	26 (0.9)	15 (57.7)	11 (42.3)	0.027
No	2927 (99.1)	2233 (76.3)	694 (23.7)	
HIV-positive (n=2952)				
Yes	110 (3.7)	77 (70.0)	33 (30.0)	0.125
No	2842 (96.3)	2170 (76.4)	672 (23.6)	
Diabetes (n=2953)				
Yes	817 (27.7)	580 (71.0)	237 (29.0)	<0.001
No	2136 (72.3)	1668 (78.1)	468 (21.9)	
Chronic kidney disease (n=2953)				
Yes	105 (3.6)	76 (72.4)	29 (27.6)	0.359
No	2848 (96.4)	2172 (76.3)	676 (23.7)	
Chronic liver disease (n=2953)				
Yes	205 (6.9)	145 (70.7)	60 (29.3)	0.060
No	2748 (93.1)	2103 (76.5)	645 (23.5)	
TB site (n=2953)				
Pulmonary	2278 (77.1)	1753 (77.0)	525 (23.0)	0.124
Extrapulmonary	392 (13.3)	291 (74.2)	101 (25.8)	
Disseminated	283 (9.6)	204 (72.1)	79 (27.9)	
TB medication (n=2953)				
Fixed-dose combination	2710 (91.8)	2074 (76.5)	636 (23.5)	0.084
Individual drugs	243 (8.2)	174 (71.6)	69 (28.4)	

ADR: Adverse drug reaction; HIV: Human immunodeficiency virus; TB: Tuberculosis.

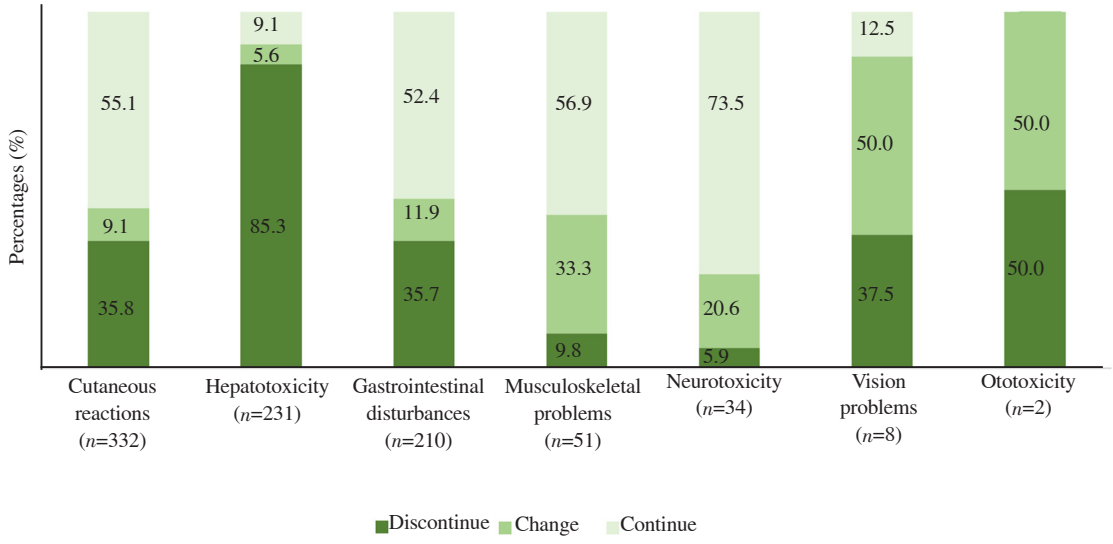

Figure 2. Management of adverse drug reactions.

observed to have a lower likelihood in all ADRs (a*OR*=0.73) and gastrointestinal disturbances (a*OR*=0.60). The highest odds of ADRs were observed among illicit drug users in all ADRs and particularly for hepatotoxicity, with approximately 2.6 and 3.8 times the risk, respectively. HIV-positive patients were shown to have 2 to 3 times the risk for all ADRs, hepatotoxicity, and gastrointestinal disturbances. Patients with concurrent diabetes experienced 1.4 times the risk for all ADRs and about 2.8 times the risk of gastrointestinal disturbances. Similarly, chronic liver disease demonstrated around 1.6 times the risk for all ADRs and 2.4 times the risk of hepatotoxicity. Unhealthy lifestyles appeared to independently affect risk, for instance, smoking was shown to have a lower risk of gastrointestinal disturbances (a*OR*=0.38), while alcohol intake was associated with a higher risk of hepatotoxicity (a*OR*=1.64), despite no significant association with all ADRs. Notably, two interaction terms were observed, with HIV-positive plus chronic liver disease reducing the risk of all ADRs (a*OR*=0.23) and hepatotoxicity (a*OR*=0.09), and age ≥60 with smoking tripling the risk of gastrointestinal disturbances (a*OR*=3.05).

3.4. Clinical impacts of adverse drug reactions

ADRs led to a median interruption of 19 days (IQR=21). The greatest impact was observed, with nearly half (49.4%) of the patients experiencing interruptions of at least 1 day and one-third (33.0%) interrupted treatment for at least 14 days (2 weeks). This also resulted in changing medications (49.5%), restarting treatment from the beginning (34.5%), and hospitalization (15.2%). However, only a minority (1.7%) was classified as loss to follow-up, with the remaining 98.3% achieving a successful treatment outcome (Figure 1). Comparisons between ADRs and no ADRs for treatment interruption, changes in medication, and restarting treatment demonstrated significant differences with $P<0.001$, but no differences were observed for the final treatment outcomes ($P=0.388$) (Table 3).

Table 2. Multiple logistic regression of factors associated with adverse drug reactions [*n* (%)].

Characteristics	All ADRs		Cutaneous reactions		Hepatotoxicity		Gastrointestinal disturbances	
	a*OR* (95% *CI*)	*P*	a*OR* (95% *CI*)	*P*	a*OR* (95% *CI*)	*P*	a*OR* (95% *CI*)	*P*
Age ≥60, years	1.68 (1.40, 2.02)	<0.001	1.57 (1.22, 2.02)	<0.001	1.46 (1.08, 1.96)	0.013	1.61 (1.17, 2.21)	0.003
Male	0.73 (0.61, 0.87)	0.001	-	-	-	-	0.60 (0.44, 0.81)	0.001
Smoking	-	-	-	-	-	-	0.38 (0.21, 0.70)	0.002
Alcohol intake	-	-	-	-	1.64 (1.02, 2.65)	0.043	-	-
Illicit drug use	2.59 (1.15, 5.83)	0.021	-	-	3.83 (1.57, 9.36)	0.003	-	-
HIV-positive	2.13 (1.35, 3.38)	0.001	-	-	2.96 (1.66, 5.27)	<0.001	2.10 (1.01, 4.37)	0.046
Diabetes	1.40 (1.16, 1.69)	<0.001	-	-	-	-	2.77 (2.07, 3.71)	<0.001
Chronic kidney disease	-	-	-	-	-	-	-	-
Chronic liver disease	1.58 (1.13, 2.21)	0.007	-	-	2.35 (1.53, 3.62)	<0.001	-	-
Interaction term		-			-	-	-	-
HIV-positive and chronic liver disease	0.23 (0.06, 0.90)	0.034	-	-	0.09 (0.01, 0.75)	0.027	-	-
Age ≥60 years and smoking	-	-	-	-	-	-	3.05 (1.27, 7.34)	0.013

ADR: Adverse drug reaction; HIV: Human immunodeficiency virus; a*OR*: Adjusted odds ratio; *CI*: Confidence interval.

Table 3. Clinical impacts of adverse drug reactions [*n* (%)].

Clinical impacts	Total (*n*=2953)	No ADR (*n*=2248)	ADR (*n*=705)	*P* value
Interruption ≥14 days				
Yes	475 (16.1)	201 (8.9)	274 (38.9)	<0.001
No	2478 (83.9)	2047 (91.1)	431 (61.1)	
Change medicine				
Yes	349 (11.8)	0 (0.0)	349 (49.5)	<0.001
No	2604 (88.2)	2248 (100.0)	356 (50.5)	
Treatment restart				
Yes	314 (10.6)	71 (3.2)	243 (34.5)	<0.001
No	2639 (89.4)	2177 (96.8)	462 (65.5)	
Treatment outcome				
Success	2886 (97.7)	2193 (97.6)	693 (98.3)	0.388
Loss to follow-up	64 (2.2)	52 (2.3)	12 (1.7)	
Failure	3 (0.1)	3 (0.1)	0 (0.0)	

ADR: Adverse drug reaction.

4. Discussion

The four first-line antitubercular drugs have been used since the 1980s to treat TB infection[16]. Despite decades of usage, the occurrence of ADRs remains unpredictable and adds to the complexity of TB management. In Malaysia, national data indicated the underreporting of adverse events for antitubercular drugs, rendering the rates unknown[13]. About one-quarter (23.9%) of the present cohort experienced at least one occasion of ADR, comparable to 35.7% in another study conducted in Malaysia[17]. Notably, there was a wide variation in ADR prevalence ranging between 8%-85% globally due to different study designs and methodologies[6].

The predominant ADRs in our present cohort were similar to those reported in another study conducted in the Penang State, encompassing cutaneous reactions, hepatotoxicity, and gastrointestinal disturbances[17]. Studies have shown that ADRs commonly occur in the intensive phase, within the first 2 months of treatment initiation[6,17]. This was supported by the onset of six out of seven ADRs observed during the intensive phase. More vigilant monitoring should be conducted during the first 2 weeks of treatment, as most ADRs, including cutaneous reactions, hepatotoxicity, gastrointestinal disturbances, and vision problems, occurred around 2 weeks of initiation in our study. Given the myriad presentations, a high index of suspicion is necessary for early detection and management[13].

Management of ADRs is determined by the severity of disease and reactions. In the present cohort, the discontinuation of antitubercular drugs was mostly observed in cases of hepatotoxicity. Hepatotoxicity is commonly caused by isoniazid, rifampicin, and pyrazinamide, necessitating the discontinuation of these drugs, followed by a gradual rechallenge[13]. Among these, hepatotoxicity induced by pyrazinamide was relatively more frequent than with other first-line antitubercular drugs[18,19]. The majority of ADRs related to cutaneous reactions, gastrointestinal disturbances, musculoskeletal problems, and neuropathy were manageable with the continuation of therapy-most of the time, symptomatic treatment was adequate, and providing simple advice, such as changing the timing of administration to post-meal could alleviate gastrointestinal symptoms[6]. Meanwhile, vision problems most frequently led to direct modification of the treatment regimen in the present study. Ethambutol, as the presumed offending drug would be withheld while maintaining isoniazid, rifampicin, and pyrazinamide. As per the guideline, an alternative regimen should contain at least three or two effective drugs in the intensive and continuation phases, respectively, with the duration of treatment varying depending on the regimen[13].

The knowledge of potential adverse events related to individual drugs and the causality assessment of ADRs are both important to avoid unnecessary treatment interruptions[20]. All first-line antitubercular drugs have the potential to cause cutaneous reactions and gastrointestinal disturbances, while hepatotoxicity may be caused by three drugs (isoniazid, rifampicin, and pyrazinamide), requiring gradual re-challenge of each drug to identify the offending agent[6,13]. Knowledge of specific drug-induced reactions, such as isoniazid-induced peripheral neuropathy, pyrazinamide-induced hyperuricemia and arthralgia, and vision disturbances due to ethambutol, facilitates relatively easier management to avoid unnecessary discontinuation of other essential components that could compromise treatment[6]. Isoniazid and rifampicin have been reported to cause ototoxicity[21], although such incidences are rare as only two cases were reported in our study. Causality assessment involves investigating the relationship of ADR onset with drug intake, concurrent diseases, and medications including traditional medications or supplements, coupled with objective evidence if applicable, to establish a causal relationship between ADR occurrence and the suspected offending drug[22]. Additionally, providing detailed explanations regarding ADRs, along with monitoring and management strategies, and using effective counseling skills with a patient-centered approach, are essential to ensure medication adherence[20].

Risk factors differ according to the types of ADRs. Overall, the elderly, females, illicit drug users, and individuals with underlying HIV-positive status, diabetes, and chronic liver disease demonstrated an increased risk of ADRs with antitubercular drugs. This finding aligns with studies conducted in Brazil and Korea, indicating that older TB patients, females, and those with comorbidities pose a higher risk of ADRs[18,23]. Regarding individual ADRs, our data showed that the female sex was associated with a higher risk of gastrointestinal disturbances, while another study demonstrated a higher risk of hepatotoxicity[24]. Patients with underlying diabetes also commonly experienced gastrointestinal problems, although not statistically significant[25]. Serious adverse events were reported among TB-HIV coinfected patients, particularly peripheral neuropathy and persistent vomiting, but no differences in hepatotoxicity compared to those without HIV coinfection[26]. In contrast, our study demonstrated 2-3 times the risk of gastrointestinal disturbances and hepatotoxicity among HIV-coinfected patients. Of note, alcohol intake and chronic liver disease were associated with an increased risk of hepatotoxicity, which was in concordance with a study done by Song *et al*[27]. Underlying comorbidities with concurrent medications, and alcohol consumption potentially augment antitubercular drug reactions resulting in the occurrence of adverse events[28]. Closer monitoring, such as earlier and more frequent liver function tests, is warranted in these high-risk groups of patients to enable early detection and prompt management of ADRs.

The impact of ADRs on treatment interruption for at least 2 weeks, followed by restarting treatment from the beginning, was observed in approximately one-third of the population in the present cohort. In cases of interruptions exceeding 2 weeks in the intensive phase,

TB treatment generally has to be restarted due to high bacillary loads and an increased chance of developing drug resistance[4]. Longer interruption periods were also exhibited among those experiencing hepatotoxicity[27], similar to our study with significant differences observed in interruptions ≥2 weeks among those experiencing ADRs. Nonetheless, there were no significant differences in the final treatment outcomes, with only a minority eventually interrupting treatment in the present cohort.

Limitations of this study included the exclusion of death and transfer-out cases due to incomplete documentation and substantial missing data. Additionally, there was no causality assessment to classify the likelihood of the adverse event with the drug, as it is not a routine practice in our setting. Most of the ADRs were not officially reported for pharmacovigilance, making it impossible to retrieve all necessary information for post-causality assessment due to the retrospective study design. As such, there could be differing individual judgments between the assessors, which might suggest an unlikely ADR secondary to antitubercular drugs but be documented instead. Furthermore, there was no reported grading for ADR severity. However, conditions requiring hospitalization for further monitoring and treatment could imply a severe condition of at least Grade 3, based on the Common Terminology Criteria for Adverse Events (CTCAE)[29], experienced by 15.2% of those involved.

In conclusion, this study showed that the occurrence of ADRs was most common in the first 2 weeks of treatment initiation. Generally, the older population (≥60 years) had a higher risk of ADRs across overall and individual ADRs investigated, namely cutaneous reactions, hepatotoxicity, and gastrointestinal disturbances. Other predictive factors were females, illicit drug use, and comorbidities such as HIV-positive status, diabetes, and chronic liver disease. Alcohol intake independently increased the risk of hepatotoxicity despite not affecting the risk for all ADRs. Treatment discontinuation was mostly observed in cases of hepatotoxicity. ADRs resulted in TB treatment interruptions, changes in medications, treatment restarts, and hospitalizations. Therefore, to minimize the clinical impacts, identifying ADRs among high-risk groups is essential to enable close monitoring, early detection, and timely management of adverse events. Proactive reporting of ADRs is highly encouraged for pharmacovigilance to improve drug safety and overall quality of healthcare.

Conflict of interest statement

All authors declare that there is no conflict of interest.

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Authors' contributions

ALO, MMB, FI, CYT, SKC, and STT conceptualized the study. ALO conducted the study, analyzed the data, and performed the initial write-up of the study. MMB was involved in data analysis and verification. FI was involved in data verification. Additional inputs were obtained from all authors to improve the final write-up of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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