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Original article

Tuberculosis treatment-related adverse events and associated risk factors: Insights from a retrospective cohort in Morocco

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Abstract. *Background and aim:* Tuberculosis (TB) continues to be a substantial global health concern. Treatment for TB typically involves a regimen of multiple drugs. Although first-line anti-TB medications are generally effective, the associated side effects (SE) can cause significant morbidity and may even hinder treatment adherence. This study seeks to assess the side effects of first-line anti-TB drugs in individuals aged 18 to 55 years attending the pneumo-phthisiology department in the Gharb Region of Morocco. *Methods:* This retrospective study was conducted in the province of Kenitra, Morocco. Data were collected from 189 participants using a simple random sampling method. Two binary logistic models were developed for this study. The first model examined the effect of sociodemographic factors on side effects of antitubercular drugs. The second model investigated the effect of sociodemographic factors on the risk of treatment discontinuation or modification among patients. *Results:* Among the patients, 37.0% experienced AEs, with the most common being cutaneous (38.57%), gastrointestinal (22.86%), and neurological (10%). Additionally, 21.7% discontinued or modified their treatment. The intensive treatment phase and the first week of therapy were critical periods for the onset of AEs and treatment interruptions. Logistic regression identified several risk factors. Female gender, low socioeconomic status, rural origin, and diabetes were significantly associated with an increased risk of AEs and treatment discontinuation. Conversely, university education and age groups of 26–36 and 37–55 years were protective factors against treatment interruptions. Patients with diabetes had an 8-fold increased risk of AEs, while early AEs (<1 week) significantly heightened the likelihood of treatment discontinuation. *Conclusions :* This study emphasizes the need for enhanced monitoring during the intensive phase, particularly in the early weeks, to mitigate risks. Tailored strategies addressing high-risk groups, such as women, socioeconomically disadvantaged individuals, and those with diabetes, are crucial to improving treatment adherence and outcomes. (www.actabiomedica.it)

Key words: tuberculosis, antitubercular agents, adverse drug reactions, drug-related side effects and adverse reactions, risk factors, retrospective studies, Morocco, hospital-based study

Introduction

Tuberculosis (TB), an infectious disease caused by *Mycobacterium tuberculosis*, remains a significant global public health challenge (1). The World Health Organization (WHO) reported that in 2020, 10 million people were affected by tuberculosis, and 1.5 million died from it (2). Despite the effectiveness of first-line anti-tuberculosis drugs, the associated side effects (SE) of these treatments lead to significant

morbidity and can even compromise their effectiveness. Side effects can result in treatment discontinuation, thereby increasing the risk of therapeutic failure and mortality (3). The global prevalence of SE related to anti- tuberculosis drugs, especially first-line drugs, varies significantly, ranging from 8% to 83.5% (4). In Morocco, a country with an intermediate prevalence of tuberculosis, an estimated 30,897 cases were reported in 2017, which is approximately 88 cases per 100,000 inhabitants (5). Since 1991, the tuberculosis control program in Morocco has adopted strategies such as Directly Observed Treatment Short Course (DOTS) and more recently the stop TB strategy, demonstrating a commitment to managing this disease (6). Tuberculosis treatment relies on a combination of drugs, including isoniazid, rifampicin, pyrazinamide, and ethambutol, administered over an extended period of at least 6 months. This drug combination is known for its potential side effects and their increased severity in combination. Concerns about the frequency and severity of SE are also relevant in the context of this therapeutic combination. Among these, comorbidities such as diabetes have been identified as critical risk factors exacerbating the severity of drug-induced side effects and leading to treatment interruptions. Additionally, the intensive phase of treatment, characterized by a high drug burden, is particularly associated with an increased incidence of adverse effects, highlighting the importance of early monitoring during this period. Moreover, the occurrence of early adverse effects within the first week of treatment has emerged as a significant factor linked to both the discontinuation of treatment and the need for modifications, underscoring the necessity for prompt detection and management (2,7). This study aims to evaluate the side effects of first-line anti-tuberculosis drugs in individuals aged 18 to 55 years attending the pneumophthysiology department of CHP Kenitra-Morocco. The analysis focuses on identifying risk factors associated with treatment discontinuation or modification, as well as side effects. By incorporating critical factors such as comorbidities, the timing of side effects, and the challenges of the intensive treatment phase, this study provides a comprehensive understanding of the risks and potential strategies to improve adherence and outcomes. The results of this study will help better understand the challenges related to managing side effects and develop more effective management strategies to improve therapeutic outcomes and reduce the impact of tuberculosis on the Moroccan population.

Methods

Study subject and location

This retrospective study was conducted in the province of Kenitra, Morocco. This province is situated in a region predominantly inhabited by an economically disadvantaged population. Data were collected from 189 participants using a simple random sampling method. Each participant completed a consent form based on the surveillance sheet.

Study variables

The molecules administered to subjects with tuberculosis include Isoniazid, Rifampicin, Ethambutol, and Pyrazinamide. Regarding the variable of side effects related to antitubercular drugs, we initially collected side effects by type (digestive, cutaneous, hematological, neurological, hepatic, cardiovascular, ENT/ocular, and others). Then, during the multivariate analysis, the different types were treated as a binary response, coded as 1 for the risk of side effects of antitubercular drugs in the comprehensive models, 1 for individuals experiencing side effects, and 0 otherwise. Regarding the discontinuation or modification of the treatment administered to the subjects (temporary discontinuation, permanent discontinuation, treatment change), the socioeconomic status variable was determined based on the poverty threshold set by the High Commission for Planning, where an income of less than 3 000 MAD (300 Dollars) per month was considered a low socioeconomic status (8).

Multivariate logistic models

In this study, two binary logistic models were developed. The first model aimed to examine the effect

of sociodemographic factors on side effects of antitubercular drugs. In the second model, we investigated the effect of sociodemographic factors on the risk of treatment discontinuation or modification in patients.

Biases

During the study's design and results analysis, three types of biases were considered to mitigate their effects and implications on our conclusions. Selection biases, which could distort the representation of the source and/or target population, were addressed to minimize any underestimation of the parameter of interest (9). Similarly, classification biases were controlled by a prior verification of the patients in our sample before their classification based on the exposure or risk under study, in order to avoid any distortion of reality (10). Furthermore, the phenomenon of confounding was taken into account in the multivariate logistic analysis to manage potential confounding biases (11).

Inclusion and exclusion criteria

All patients with tuberculosis, regardless of the form of the disease, as well as all age groups and genders, were included if they were undergoing treatment at the pneumo-phtysiology department of El IDRISSI Hospital in Kenitra and at the CDTMR, and if they exhibited side effects related to anti-tuberculosis medications. Patients who did not exhibit side effects related to antitubercular drugs were excluded from this study.

Ethical consideration

The study received formal approval from the Directorate of the Higher Institute of Nursing and Health Technical Professions, Annex Kenitra, as well as the Provincial Hospital Directorate of El Idrissi Kenitra. Written informed consent was obtained from all participants prior to inclusion in the study. The research adhered to the principles outlined in the Declaration of Helsinki, ensuring compliance with international ethical standards.

Data collection

Out of 200 subjects meeting the inclusion criteria, 189 were selected for the study. Participants completed a standardized and previously validated questionnaire that gathered information on sociodemographic characteristics (origin, education level, socioeconomic status, gender, and age), current treatment, types of adverse effects, and treatment discontinuation or modification. Additionally, the questionnaire included data on comorbidity (presence of diabetes), treatment phase (intensive or continuation phase), duration before the onset of side effects (immediate <1 week, 1–2 months, >2 months), and knowledge of side effects (no knowledge, limited knowledge, sufficient knowledge).

Statistical data analysis

The questionnaire data were tabulated in Microsoft Excel, cleaned, and then exported to the statistical software Stata (StataCorp LLC, 4905 Lakeway Drive, College Station, TX 77845, USA) for analysis. Descriptive statistics were calculated and expressed as frequencies and percentages for categorical data. In bivariate analysis, the Chi-square test was used to compare qualitative variables, while Fisher's exact test was applied in the case of dichotomous variables or samples with fewer than 5 cases. A "p" value ≤ 0.05 was considered statistically significant. For binary logistic modeling, initial variables were selected based on acquired knowledge and a literature search. Variables potentially related to side effects or treatment discontinuation/modification were introduced into logistic regression models. A thorough literature review was conducted beforehand. Variables were chosen based on their clinical relevance and known or presumed confounding factors (4). Significant variables from univariate analysis were included in an initial multiple logistic regression model, with a significance threshold of 0.20, to account for potential confounding factors and interactions. To determine the best model, a three-step approach was favored: (1) specification of variables, (2) evaluation of interactions, and (3) assessment of confounding factors, followed by an assessment of accuracy. Univariate analysis in binary

logistic regression was conducted to test the association between each independent variable (sociodemographic factors) and the dependent variable (side effect or treatment discontinuation/modification). Significant variables were then subjected to binomial multiple logistic regression using the "enter" method to test independent risk factors among the variables. Model fit was assessed with the Hosmer-Lemeshow goodness-of-fit test, and odds ratios were calculated. The significance threshold was set at 95% ($p \leq 0.05$), and results were presented in tabular form.

Results

Descriptive analysis

A total of 189 subjects aged 18 to 55 years were included in the study, with a mean age of 34.46 ± 10.68 years. Among these subjects, 41 (21.7%) discontinued or modified their treatment due to side effects, and 70 (37.0%) reported side effects related to antitubercular drugs. Descriptive analysis of side effects by type revealed that cutaneous effects (38.57%) and digestive effects (22.86%) were the most frequent in our study, followed by neurological effects (10%). Other types of side effects, such as hematological effects (7.143%), ENT/ocular effects (4.286%), cardiovascular effects (2.857%), hepatic effects, and others, were also reported (Figure 1).

Analysis of side effects related to antitubercular drugs based on socioeconomic status and origin revealed a significantly higher frequency of side effects among subjects from rural backgrounds with low socioeconomic status (65% vs. 35%, $p < 0.05$). Conversely, a significantly lower risk was observed among subjects with a medium or high socioeconomic status (Figure 2 and Figure 3).

The Chi-square analysis (Table 1) revealed significant associations between the occurrence of adverse effects and several variables. Among the 189 patients included, 37.0% reported adverse effects, with a predominance among women (75.7%, $p < 0.001$) and patients from rural areas (80.0%, $p = 0.015$). Regarding education level, 41.4% of illiterate patients reported adverse effects, compared to only 8.6% of patients with a university-level education ($p < 0.001$). Participants with low socioeconomic status were significantly more affected (68.6%, $p < 0.001$). Furthermore, the age group of 18–25 years was the most impacted (57.1%,

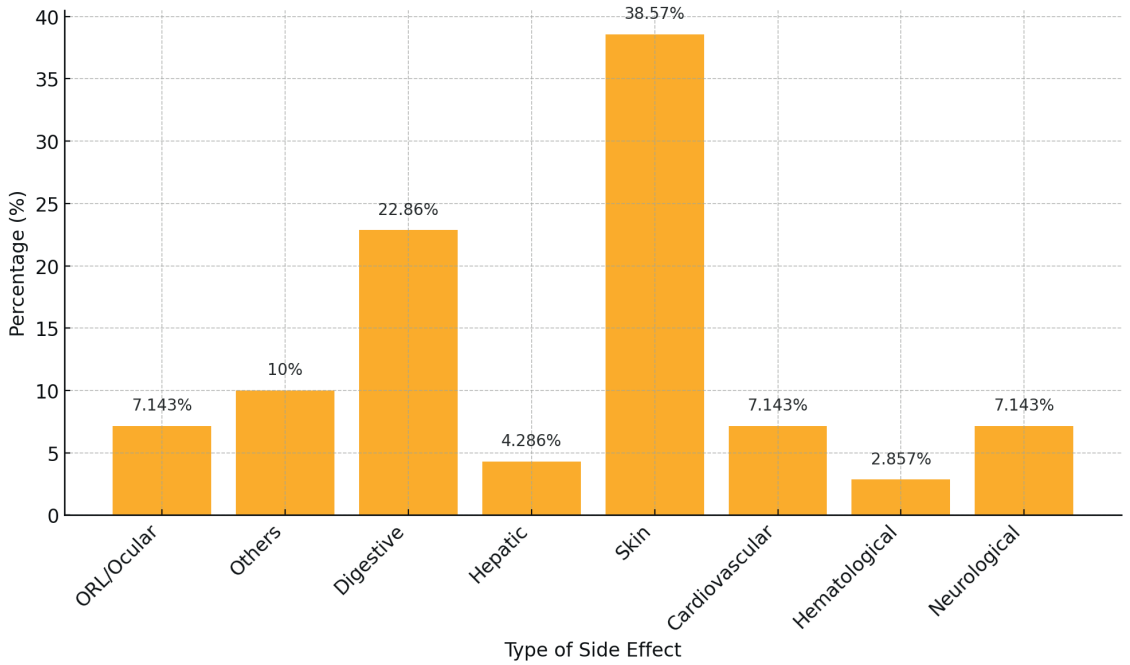

Figure 1. Distribution of side effects by type.

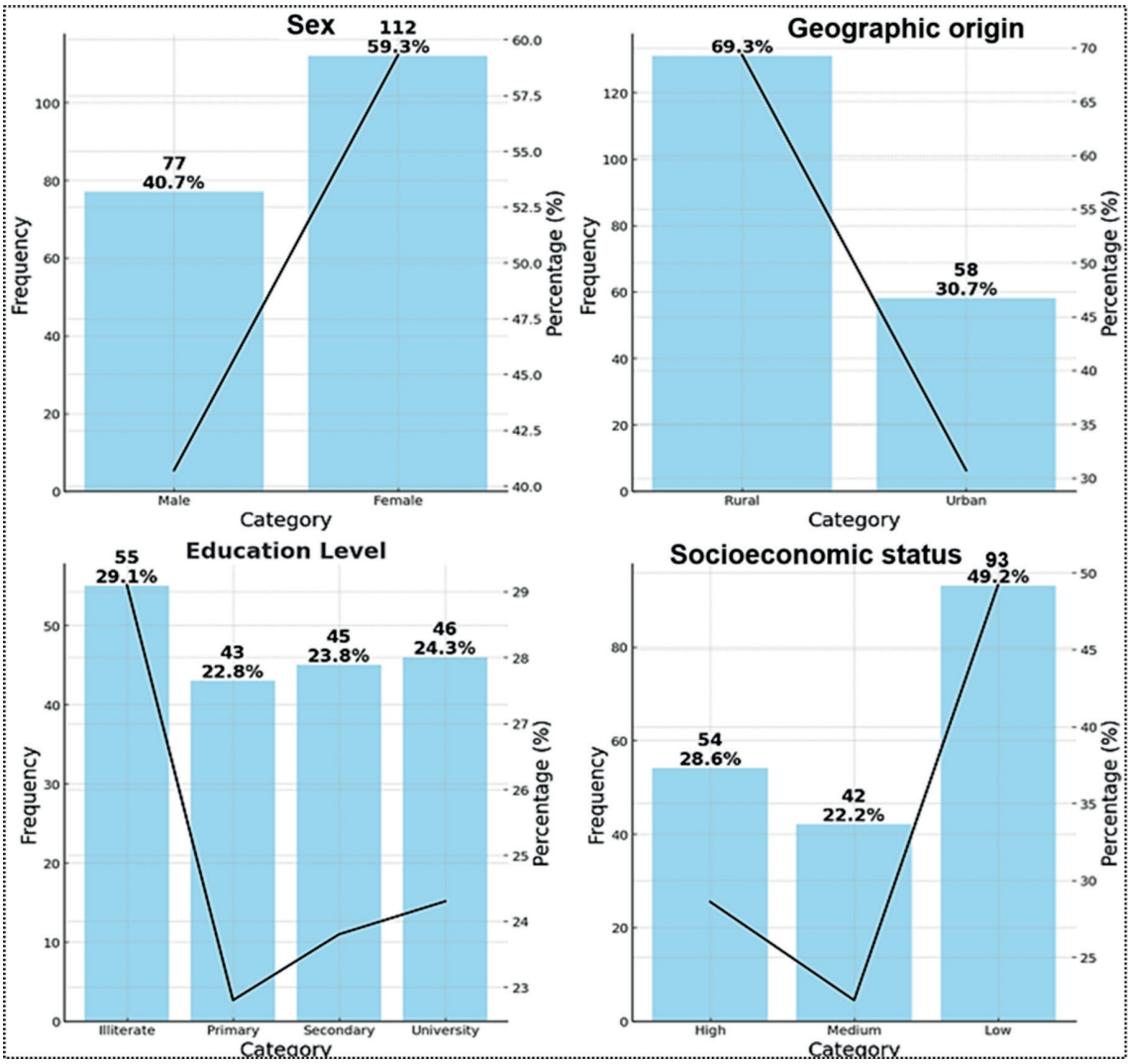

Figure 2. Distribution of Patients by Gender, Origin, Education, and Socioeconomic Status.

$p < 0.001$), as well as patients with diabetes (47.1%, $p < 0.001$). Adverse effects were more frequent among patients in the intensive treatment phase (54.3%, $p < 0.001$) and often occurred within the first week of treatment (38.6%, $p < 0.001$) (Table 1).

The logistic regression analysis (Table 2) identified several independent factors associated with adverse effects. Women were at increased risk (AOR = 2.78, 95% CI [1.038–7.464], $p < 0.05$), as were patients with low socioeconomic status (AOR = 3.81, 95% CI [1.131–12.840], $p < 0.05$). In contrast, urban origins (AOR = 0.23, 95% CI [0.077–0.700], $p < 0.01$) and secondary or university education levels (AOR = 0.40, 95% CI [0.105–1.536]) were protective factors. Regarding age, patients aged 26–36 years (AOR = 0.21, 95% CI [0.058–0.776], $p < 0.05$) and 37–55 years (AOR = 0.16, 95% CI [0.054–0.473], $p < 0.01$) were significantly less exposed. Finally, diabetes comorbidity was strongly associated with an increased risk of adverse effects (AOR = 8.15, 95% CI [2.555–26.007], $p < 0.001$). Patients in the continuation phase had a reduced risk (AOR = 0.30, 95% CI [0.112–0.845], $p < 0.05$), while the immediate occurrence of adverse effects during the first week significantly increased the risk (AOR = 8.39, 95% CI [2.274–30.984], $p < 0.01$).

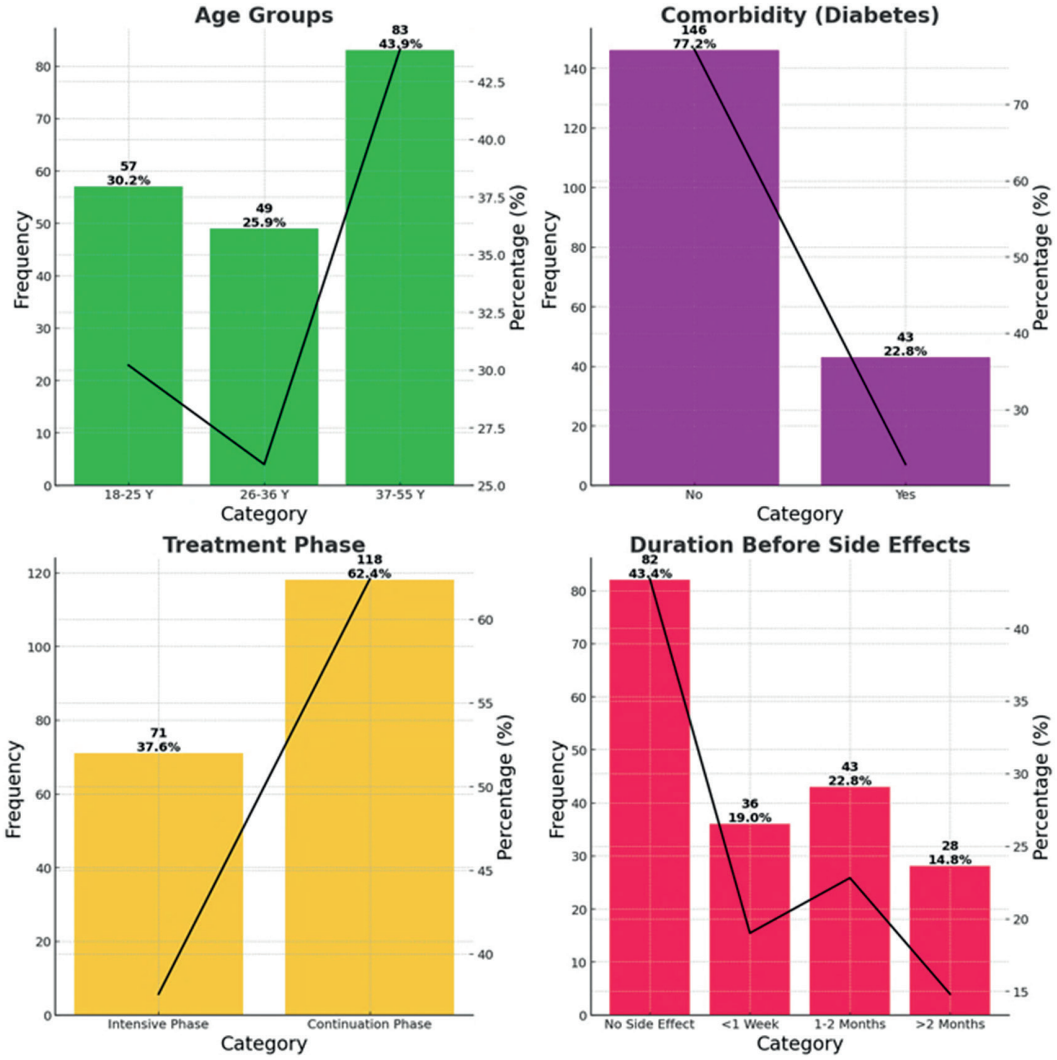

Figure 3. Distribution of Patients by Age, Comorbidity, Treatment Phase, and Duration Before Side Effects.

Chi-square analysis (Table 3) revealed that 21.7% of patients interrupted or modified their treatment. Significantly higher rates of treatment interruption/modification were observed among women (87.8%, $p < 0.001$), patients from rural areas (82.9%, $p = 0.033$), illiterate patients (46.3% vs. 2.4% for university-educated, $p < 0.001$), and those with low socioeconomic status (73.2%, $p = 0.002$). Young adults aged 18-25 years (65.9%, $p < 0.001$), patients with diabetes (58.5%, $p < 0.001$), and individuals in the intensive treatment phase (63.4%, $p < 0.001$) also exhibited higher risks. Notably, 46.3% of patients reported an immediate interruption (less than 1 week) compared to only 4.9% during the continuation phase (greater than 2 months, $p < 0.001$).

The logistic regression analysis (Table 4) confirms that women have a significantly increased risk of treatment interruption or modification (AOR = 6.60, 95% CI [1.631–26.382], $p < 0.01$), as do patients with low socioeconomic status (AOR = 3.06, 95% CI [0.667–14.027]) and those with diabetes (AOR = 6.07, 95% CI [1.829–20.152], $p < 0.01$). Conversely, a university level of education (AOR = 0.09, 95% CI [0.008–1.025]), urban origin (AOR = 0.27, 95% CI [0.067–1.103]), and age groups of 26–36 years (AOR = 0.62, 95% CI [0.146–2.595]) and 37–55 years (AOR = 0.20, 95% CI [0.056–0.737], $p < 0.05$) are associated with a reduced risk. Finally, patients in the continuation phase exhibit a reduced risk of interruption (AOR = 0.23, 95% CI [0.071–0.762], $p < 0.05$), while those

Table 1. Sociodemographic risk factors associated with treatment discontinuation or modification in patients.

Occurrence of Adverse Effects				
	Yes	**No**	**Total**	**p-value**
Effectif (N=189)	119 (63.0%)	70 (37.0%)	189 (100.0%)	
Sex				
Male	60 (50.4%)	17 (24.3%)	77 (40.7%)	<0.001
Female	59 (49.6%)	53 (75.7%)	112 (59.3%)	
Geographic origin				
Rural	75 (63.0%)	56 (80.0%)	131 (69.3%)	0.015
Urban	44 (37.0%)	14 (20.0%)	58 (30.7%)	
Education level				
Illiterate	26 (21.8%)	29 (41.4%)	55 (29.1%)	<0.001
Primary	21 (17.6%)	22 (31.4%)	43 (22.8%)	
Secondary	32 (26.9%)	13 (18.6%)	45 (23.8%)	
University	40 (33.6%)	6 (8.6%)	46 (24.3%)	
Statut socio-économique				
High (>5000 DH/month)	44 (37.0%)	10 (14.3%)	54 (28.6%)	<0.001
Medium (3000–5000 DH/month)	30 (25.2%)	12 (17.1%)	42 (22.2%)	
Low (<3000 DH/month)	45 (37.8%)	48 (68.6%)	93 (49.2%)	
Age				
18–25 years	17 (14.3%)	40 (57.1%)	57 (30.2%)	<0.001
26–36 years	37 (31.1%)	12 (17.1%)	49 (25.9%)	
37–55 years	65 (54.6%)	18 (25.7%)	83 (43.9%)	
Comorbidity (Diabetes)				
No (absence of diabetes)	109 (91.6%)	37 (52.9%)	146 (77.2%)	<0.001
Yes (Presence of diabetes)	10 (8.4%)	33 (47.1%)	43 (22.8%)	
Treatment phase				
Intensive phase	33 (27.7%)	38 (54.3%)	71 (37.6%)	<0.001
Continuation phase	86 (72.3%)	32 (45.7%)	118 (62.4%)	
Time before adverse effects				
No effects	63 (52.9%)	19 (27.1%)	82 (43.4%)	<0.001
Immediate (<1 week)	9 (7.6%)	27 (38.6%)	36 (19.0%)	
Early in treatment (1–2 months)	26 (21.8%)	17 (24.3%)	43 (22.8%)	
Continuation phase (>2 months)	21 (17.6%)	7 (10.0%)	28 (14.8%)	
Distance to treatment center				
<10 km	26 (21.8%)	24 (34.3%)	50 (26.5%)	0.171
10-30 km	50 (42.0%)	24 (34.3%)	74 (39.2%)	
>30 km	43 (36.1%)	22 (31.4%)	65 (34.4%)	
Professional status				
Unemployed	36 (30.3%)	24 (34.3%)	60 (31.7%)	0.282
Informal employment	32 (26.9%)	24 (34.3%)	56 (29.6%)	
Stable employment	51 (42.9%)	22 (31.4%)	73 (38.6%)	
Knowledge of adverse effects				
No knowledge	39 (32.8%)	38 (54.3%)	77 (40.7%)	0.014
Limited knowledge,	42 (35.3%)	18 (25.7%)	60 (31.7%)	
Sufficient knowledge	38 (31.9%)	14 (20.0%)	52 (27.5%)	

Abbreviations: COR: Crude odds ratio, AOR: Adjusted Odds ratio, CI: Confidence interval, -ref: Reference group, * : Significant p-value.

Table 2. Independent Risk Factors Associated with the Occurrence of Adverse Effects Related to Antitubercular Drugs (Logistic Regression Analysis).

Occurrence of Adverse Effects				
Risk Factors	**COR**	**95% CI**	**AOR**	**95% CI**
Sex				
Male	Ref.		Ref.	
Female	3.17**	1.648-6.096	2.78*	1.038-7.464
Geographic orgin				
Rural	Ref.		Ref.	
Urban	0.42*	0.212-0.852	0.23**	0.077-0.700
Education Level				
Illiterate	Ref.		Ref.	
Primairy	0.93	0.422-2.087	2.56	0.746-8.831
Secondary	0.36*	0.158-0.838	0.57	0.161-2.057
University	0.13***	0.049-0.368	0.40	0.105-1.536
Socio-economic status				
High (>5000 DH/month)	Ref.		Ref.	
Medium (3000-5000 DH/month)	1.76	0.674-4.591	3.45	0.869-13.757
Low (<3000 DH/month)	4.69***	2.113-10.424	3.81*	1.131-12.840
Age				
18-25 years	Ref.		Ref.	
26-36 years	0.13***	0.058-0.326	0.21*	0.058-0.776
37-55 years	0.11***	0.054-0.254	0.16**	0.054-0.473
Comorbidity (Diabetes)				
Non (absence of diabetes)	Ref.		Ref.	
Yes (presence de diabetes)	9.72***	4.369-21.630	8.15***	2.555-26.007
Treatment Phase				
Intensive phase	Ref.		Ref.	
Continuation phase	0.32***	0.174-0.599	0.30*	0.112-0.845
Time before adverse effects				
No effects	Ref.		Ref.	
Immediate (<1 week)	9.94***	3.994-24.768	8.39**	2.274-30.984
Early in tratment (1-2 months)	2.16	0.976-4.815	1.30	0.401-4.226
Continuation phase (>2 months)	1.10	0.407-2.996	1.48	0.388-5.647
Knowledge of adverse effects				
No knowledge	Ref.		Ref.	
Limited Knowledge	0.43*	0.216-0.894	0.46	0.155-1.349
Sufficient Knowledge	0.37*	0.177-0.807	0.45	0.132-1.539

Abbreviations: COR: Crude odds ratio, AOR: Adjusted Odds ratio, CI: Confidence interval, -ref: Reference group, * : Significant p-value.

Table 3. Analysis of Sociodemographic Factors Associated with Treatment Interruption or Modification (Chi-square Analysis).

Treatment Interruption/Modification				
	Traitement maintenu	**Traitement interrompu/modifié**	**Total**	**p-value**
Effectif (N=189)	148 (78.3%)	41 (21.7%)	189 (100.0%)	
Sex				
Male	72 (48.6%)	5 (12.2%)	77 (40.7%)	<0.001
Female	76 (51.4%)	36 (87.8%)	112 (59.3%)	
Geographic origin				
Rural	97 (65.5%)	34 (82.9%)	131 (69.3%)	0.033
Urban	51 (34.5%)	7 (17.1%)	58 (30.7%)	
Education Level				
Illiterate	36 (24.3%)	19 (46.3%)	55 (29.1%)	<0.001
Primairy	29 (19.6%)	14 (34.1%)	43 (22.8%)	
Secondary	38 (25.7%)	7 (17.1%)	45 (23.8%)	
University	45 (30.4%)	1 (2.4%)	46 (24.3%)	
Socio-economic status				
High (>5000 DH/month)	49 (33.1%)	5 (12.2%)	54 (28.6%)	0.002
Medium (3000-5000 DH/month)	36 (24.3%)	6 (14.6%)	42 (22.2%)	
Low (<3000 DH/month)	63 (42.6%)	30 (73.2%)	93 (49.2%)	
Age				
18-25 years	30 (20.3%)	27 (65.9%)	57 (30.2%)	<0.001
26-36 years	43 (29.1%)	6 (14.6%)	49 (25.9%)	
37-55 years	75 (50.7%)	8 (19.5%)	83 (43.9%)	
Comorbidity (Diabetes)				
Non (absence of diabetes)	129 (87.2%)	17 (41.5%)	146 (77.2%)	<0.001
Yes (presence of diabetes)	19 (12.8%)	24 (58.5%)	43 (22.8%)	
Treatment phase				
Intensive phase	45 (30.4%)	26 (63.4%)	71 (37.6%)	<0.001
Continuation phase	103 (69.6%)	15 (36.6%)	118 (62.4%)	
Time before adverse effects				
No effects	73 (49.3%)	9 (22.0%)	82 (43.4%)	<0.001
Immediate (<1 week)	17 (11.5%)	19 (46.3%)	36 (19.0%)	
Early in treatment (1-2 months)	32 (21.6%)	11 (26.8%)	43 (22.8%)	
Continuation phase (>2 months)	26 (17.6%)	2 (4.9%)	28 (14.8%)	
Distance to tratment centre				
<10 km	40 (27.0%)	10 (24.4%)	50 (26.5%)	0.779
10-30 km	59 (39.9%)	15 (36.6%)	74 (39.2%)	
>30 km	49 (33.1%)	16 (39.0%)	65 (34.4%)	

Table 3. Analysis of Sociodemographic Factors Associated with Treatment Interruption or Modification (Chi-square Analysis).

	Treatment Interruption/Modification			
	Traitement maintenu	**Traitement interrompu/modifié**	**Total**	**p-value**
Professional status				
Unemployed	44 (29.7%)	16 (39.0%)	60 (31.7%)	0.210
Informal employment	42 (28.4%)	14 (34.1%)	56 (29.6%)	
Stable employment	62 (41.9%)	11 (26.8%)	73 (38.6%)	
Knowledge of adverse effects				
No knowledge	56 (37.8%)	21 (51.2%)	77 (40.7%)	0.175
Limited knowledge	47 (31.8%)	13 (31.7%)	60 (31.7%)	
Sufficient knowledge	45 (30.4%)	7 (17.1%)	52 (27.5%)	

experiencing immediate interruption (<1 week) have a significantly increased risk (AOR = 5.56, 95% CI [1.420–21.788], p < 0.01).

Discussion

In total, 189 patients were recruited in this study; among them, 70 patients (37.0%) developed one or more adverse effects related to first-line antitubercular drugs. Data regarding the global prevalence of adverse effects associated with first-line antitubercular drugs are scarce. According to a systematic review conducted by (4), the overall prevalence of adverse effects related to these drugs ranged from 8.4% to 83.5%. Thus, a significant variation in the prevalence of adverse effects is observed in different studies conducted in various locations. This variation can be attributed to several potential factors related to healthcare systems and patient-specific characteristics, such as treatment non-adherence, dropout rates, early assessment, and adverse effects management. Furthermore, differences in the definitions and terminologies of adverse effects adopted by clinicians, as well as the manner in which these effects are reported (subjectively by patients or objectively by clinicians based on clinical elements and surveillance with laboratory analyses), also contribute to this variation. Other factors, such as the presence of coexisting diseases like diabetes, hypertension, or hypothyroidism, as well as covariates including HIV co-infection and variations in the use of specific antitubercular drugs (including dosages and pharmacological interactions with other drug groups, especially antiretroviral therapy), should also be considered (4,12). Interestingly, patients reported more adverse effects than those documented by clinicians (13). This observation reflects differences in the perception of adverse effects between physicians and patients. Cutaneous adverse effects are the most frequent in our study, accounting for a proportion of 38.57%. This observation aligns with findings from numerous previous studies (14–16), which reported varying proportions ranging from 16.61% to 33.33%. Pyrazinamide stands out as the drug most commonly associated with these adverse effects of antitubercular drugs (AEs), in agreement with the conclusions of (4) and (12). However, another study conducted by (17) suggests that isoniazid and rifampicin may also play a predominant role in the occurrence of these AEs. Gastrointestinal adverse effects constitute the second most frequent adverse effect, with a proportion of 22.86%. This observation could be attributed to the high quantity of tablets (4 to 7 tablets) required for oral polychemotherapy. In a study conducted by [insert reference], gastrointestinal disturbances were observed in 12.5% of patients. Another prospective study in China reported a prevalence of 3.74% for gastrointestinal adverse effects (18). However, a proportion of 67.9% was reported in a prospective Indian study (16). It is interesting to note that Pyrazinamide is the antitubercular drug most frequently associated with these gastrointestinal AEs, which aligns with the findings of the study conducted

Table 4. Independent risk factors associated with treatment interruption or modification (Logistic regression analysis).

Treatment Interruption/Modification				
Risk Factors	**COR**	**95% CI**	**AOR**	**95% CI**
Sex				
Male	Ref.		Ref.	
Female	6.82***	2.53-18.34	6.60**	1.631-26.382
Geographic origin				
Rural	Ref.		Ref.	
Urban	0.39	0.16-0.94	0.27	0.067-1.103
Education Level				
Illiterate	Ref.		Ref.	
Primary	0.91	0.39-2.13	1.48	0.397-5.528
Secondary	0.35*	0.13-0.93	0.28	0.067-1.203
University	0.042**	0.053-0.32	0.09	0.008-1.025
Socio-economic status				
High (>5000 DH/month)	Ref.		Ref.	
Medium(3000-5000 DH/month)	1.63	0.46-5.77	6.02	0.800-45.295
Low (<3000 DH/month)	4.66**	1.68-12.91	3.06	0.667-14.027
Age				
18-25 years	Ref.		Ref.	
26-36 years	0.15***	0.057-0.42	0.62	0.146-2.595
37-55 years	0.11***	0.048-0.2	0.20*	0.056-0.737
Comorbidity (Diabetes)				
Non (absence of diabetes)	Ref.		Ref.	
Oui (presence of diabetes)	9.58***	4.36-21.03	6.07**	1.829-20.152
Treatment phase				
Intensive phase	Ref.		Ref.	
Continuation phase	0.25***	0.12-0.52	0.23*	0.071-0.762
Time before adverse effects				
No effects	Ref.		Ref.	
Immediate (<1 week)	9.06***	3.49-23.50	5.56*	1.420-21.788
Early in traitement (1-2 months)	2.78*	1.05-7.38	2.00	0.459-8.785
Continuation phase (>2 months)	0.62	0.12-3.07	0.50	0.058-4.275
Knowledge of adverse effects				
No Knowledge	Ref.		Ref.	
Limited Knowledge	0.73	0.33-1.62	2.00	0.511-7.862
Sufficient Knowledge	0.41	0.16-1.06	0.74	0.167-3.264

by (19). Our multivariate analysis revealed that diabetes is strongly associated with an increased risk of developing severe adverse effects. This finding is consistent with several studies (20,21), which suggest that diabetic patients exhibit impaired immune responses and reduced capacity to effectively metabolize antitubercular drugs (22). Consequently, these patients are more vulnerable to drug toxicity. Specific management strategies, including close monitoring and dose adjustments, when necessary, are crucial to mitigating these risks. Thirdly, we observed a frequency of 10% for adverse effects such as peripheral neuropathy and dizziness, which largely aligns with the findings of (23) and is lower than that reported in an Indian study (20%) (24). The neurotoxic effects of Isoniazid and Ethambutol are well-established, but it has been suggested that neurological manifestations may result from immunological processes triggered by the tubercle bacillus rather than solely from drug neurotoxicity (25). Our findings indicate that adverse effects are more frequent during the intensive phase of treatment. This result can be explained by the combination of multiple drugs at high doses (26), which increases the likelihood of drug-drug interactions and cumulative toxicities. A study conducted by (27,28) in Indonesia similarly reported a higher prevalence of adverse effects early in treatment, highlighting the importance of enhanced monitoring during this critical phase. The gradual reduction of drug burden during the continuation phase appears to mitigate these risks, as confirmed by our results. Approximately 7.43% of the reported adverse effects in this study were hematological, cardiovascular, or ocular in nature. However, Asian studies have reported hematological adverse effects (such as thrombocytopenia) in a range of 0.1% to 0.7%. Generally, rifampicin is the agent most frequently associated with drug-induced thrombocytopenia among antitubercular medications (29,30). Moreover, our findings reveal that the occurrence of adverse effects is particularly high during the first week of treatment. This could be attributed to early sensitization reactions to medications or errors in initial dose management. These observations align with the work of (31), which recommends intensive clinical and biological monitoring during this critical period. Rapid identification of high-risk patients could prevent treatment interruptions and improve overall therapeutic outcomes. Our findings and those of Oh et al. agree that treatment interruptions are more frequent during the intensive phase, particularly in the early weeks. This critical period is marked by a high drug burden and early adverse effects, which are major triggers for interruptions. The Malaysian study (26) similarly identifies adverse effects as a key factor, consistent with our results. However, it reports a protective role of diabetes against interruptions, whereas our analysis associates diabetes with an increased risk. This discrepancy may reflect differences in clinical management or patient contexts. The study by Prasad et al. confirms that adverse effects are frequent, particularly during the intensive phase, with severe consequences that may lead to treatment modifications or interruptions (28). Our findings align with these observations, emphasizing that early adverse effects (<1 week) significantly increase the risk of treatment interruption or modification. These effects require prompt management to prevent deterioration in therapeutic outcomes. Both studies underscore the importance of early recognition of adverse effects and intensive monitoring during the initial weeks, a critical period where patients are most vulnerable. Such an approach could reduce interruptions and optimize treatment adherence. However, it is important to note that the relationship between risk factors and side effects does not necessarily imply a direct cause-and-effect relationship. The results suggest the need for further research with larger and more diverse studies to confirm these associations and explore the underlying mechanisms more deeply. Ultimately, the identification and consideration of risk factors for side effects in the prescription and monitoring of antituberculosis medications can significantly contribute to better patient management, improved treatment adherence, and ultimately a reduction in tuberculosis-related morbidity. Ongoing efforts in this area are essential to optimize the effectiveness of tuberculosis patient care and to achieve global goals in the fight against this disease.

Conclusion

In conclusion, this study highlights the crucial importance of monitoring and managing side effects (AEs) associated with first-line anti-tuberculosis

medications used in the treatment of tuberculosis. The findings revealed a high prevalence of side effects, underscoring the need to identify risk factors associated with these effects early in treatment. Factors such as low socioeconomic status, illiteracy, female gender, specific age groups, and rural origin were identified as significant risk factors for the development of AEs. This in-depth understanding of risk factors provides a valuable opportunity to implement personalized and targeted management strategies aimed at reducing the incidence of side effects and improving treatment adherence.

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