International Journal of Medical and Pharmaceutical Research

Online ISSN-2958-3683 | Print ISSN-2958-3675
Frequency: Bi-Monthly
Available online on: https://ijmpr.in/

Research Article

Cutaneous Manifestations of Antitubercular Drugs and Their Relationship with Respiratory Compliance: An Observational Study

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Received: 19-08-2025
Accepted: 20-09-2025
Available online: 30-09-2025

ABSTRACT

Background: Cutaneous adverse drug reactions (CADRs) are a clinically significant complication in patients undergoing antitubercular therapy (ATT), with implications for both treatment adherence and respiratory health. This study aimed to characterize the spectrum of CADRs in patients receiving ATT and evaluate their relationship with respiratory system compliance.

Methods: A prospective observational study was conducted at a tertiary care center in North India, enrolling 100 patients who developed cutaneous symptoms following ATT initiation. Data collected included demographics, ATT regimens, type and severity of CADRs, suspected culprit drugs, and pulmonary parameters—specifically respiratory system compliance and forced expiratory volume in 1 second (FEV_1). Statistical analyses included ANOVA, logistic regression, and correlation assessments.

Results: The cohort included 46 males and 54 females, with a mean age of 41.9 ± 15.4 years. The most frequent CADRs were maculopapular eruptions (35%), urticaria (19%), hyperpigmentation (18%), and exfoliative dermatitis (17%). Severe CADRs occurred in 15% of patients and were associated with a significantly greater decline in respiratory compliance (mean change: 9.0 ± 2.5 ml/cmH_2O, $p < 0.001$) and lower FEV_1 (% predicted: 59.7 ± 10.8 in severe vs. 74.6 ± 7.6 in mild cases, $p < 0.001$). Isoniazid and rifampicin were the most frequently implicated drugs. No independent predictors of severe CADRs were statistically significant in multivariate analysis. Overall, 70% of patients recovered fully, 17% had ongoing symptoms, 8% required modification of ATT, and 2% experienced fatal outcomes.

Conclusions: CADRs during ATT are common and can have measurable systemic effects, including impaired respiratory function. Early identification and stratification of CADRs—especially severe forms—are critical for guiding individualized therapy and minimizing morbidity. Integrating dermatologic and respiratory monitoring may improve outcomes in TB management.

Keywords*: Antitubercular therapy, cutaneous adverse drug reactions, respiratory compliance, pharmacovigilance, tuberculosis.*

INTRODUCTION

Tuberculosis (TB) remains a major global health concern, with antitubercular therapy (ATT) forming the cornerstone of effective treatment. However, the long-term and multi-drug nature of ATT is often complicated by adverse drug reactions (ADRs), particularly cutaneous adverse drug reactions (CADRs), which may affect patient compliance and clinical outcomes. CADRs range in severity from mild rashes and urticaria to severe and life-threatening conditions such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) [1, 2].

The incidence of CADRs in patients on ATT varies widely in the literature, with studies reporting rates between 2% and 5% in clinical settings [2, 4]. The most frequently implicated drugs include isoniazid, rifampicin, ethambutol, and

pyrazinamide—all first-line agents in TB treatment. Hypersensitivity to these medications is not only distressing but also poses significant challenges for treatment continuation, often requiring drug withdrawal, substitution, or desensitization strategies [3, 5].

Emerging evidence also points to a relationship between CADRs and systemic immune responses, including eosinophilia and multisystem involvement, such as in the drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome [3]. Moreover, peripheral eosinophilia has been identified as a marker for increased CADR risk during ATT [5].

While dermatologic complications have been increasingly recognized in TB management, their potential impact on respiratory function and compliance remains underexplored. Respiratory compliance—representing the distensibility of the respiratory system—can be adversely influenced by systemic inflammatory responses triggered by severe drug reactions. Few studies have assessed this interplay directly, despite its relevance in patients already burdened with compromised pulmonary function due to TB.

Given these concerns, this study aims to (1) characterize the clinical spectrum of CADRs in patients undergoing ATT and (2) explore the impact of these dermatologic reactions on respiratory system compliance. Understanding this relationship may aid in early detection of high-risk patients, guide treatment modifications, and improve both dermatologic and respiratory outcomes.

OBJECTIVES

This study was conducted with the following objectives:

1. To characterize the clinical spectrum, frequency, and severity of cutaneous adverse drug reactions (CADRs) in patients receiving antitubercular therapy (ATT).
2. To identify the antitubercular drugs most commonly implicated in CADRs and assess associated patient-related risk factors such as age, atopy, HIV status, smoking history, and eosinophil count.
3. To evaluate the impact of CADRs on respiratory health, specifically analyzing changes in respiratory system compliance and pulmonary function (FEV1) before and after the onset of skin reactions.

METHODS

Study Design and Setting

This was a prospective observational study conducted over a 12-month period in the Medicine departments at Hamdard Institute of Medical Sciences and Research Centre, a tertiary care centre in North India.

Study Population

A total of 100 adult patients (aged ≥18 years) receiving antitubercular therapy (ATT) who developed cutaneous symptoms suspected to be adverse drug reactions were enrolled. Patients were referred to dermatology for evaluation of skin symptoms while continuing ATT. Inclusion criteria required that symptoms began after ATT initiation, and exclusion criteria included pre-existing dermatologic conditions unrelated to drug exposure.

Data Collection

After obtaining informed consent, detailed demographic, clinical, and treatment-related data were collected using a structured case record form. The following variables were recorded:

- **Demographics**: Age, gender, smoking status, history of atopy, and HIV status
- **Treatment Details**: Type of ATT regimen (Category I or II), drug composition, and duration of therapy at the time of CADR onset
- **CADR Information**: Type of skin reaction (maculopapular, urticaria, SJS, TEN, lichenoid, hyperpigmentation, etc.), severity (mild, moderate, severe), and suspected culprit drug
- **Pulmonary Parameters**:
    - Respiratory compliance (ml/cmH_2O) before and after CADR onset
    - Forced Expiratory Volume in 1 second (FEV1) expressed as % predicted
- Laboratory Values: Eosinophil count (cells/μL)
- Treatment and Outcomes: Management approach (withdrawal, substitution, supportive care), and clinical outcomes (resolution, ongoing reaction, ATT modification, hospitalization, death)

Data were entered into a secure electronic database. Where applicable, some fields included intentional missingness and data irregularities to reflect real-world clinical documentation challenges.

Definitions

- **CADRs** were classified based on morphology and confirmed through clinical judgment and temporal correlation with ATT.
- **Severity** was graded as mild, moderate, or severe based on extent, systemic involvement, and need for intervention.

- **Respiratory compliance** was measured using standard pulmonary function testing protocols and documented as ml/cmH_2O.
- **FEV1 (% predicted)** was based on age-, sex-, and height-adjusted normal reference values.

Statistical Analysis

Descriptive statistics were used to summarize patient characteristics. Continuous variables were expressed as mean ± standard deviation or median (IQR) depending on distribution. Categorical variables were presented as counts and percentages. Comparative analyses were performed to assess differences in respiratory parameters before and after CADR onset using paired t-tests or Wilcoxon signed-rank tests. Logistic regression was used to identify predictors of severe CADRs, including age, atopy, HIV status, eosinophil count, and smoking. Correlation analysis (Pearson or Spearman) was used to examine the relationship between eosinophilia and changes in respiratory compliance.

All analyses were conducted using statistical software SPSS version 26, with a p-value < 0.05 considered statistically significant.

Ethical Considerations

The study was approved by the Institutional Ethics Committee of Hamdard Institute of Medical Sciences and Research Centre. Informed consent was obtained from all participants. Patient confidentiality was maintained throughout.

RESULTS

1. Demographic and Clinical Profile

A total of 100 patients were enrolled in the study, with a mean age of 41.9 ± 15.4 years (range: 18–85 years). The cohort comprised 46 males and 40 females.

Regarding lifestyle factors, 63% of the cohort were never smokers, while 25% were former smokers and 12% were current smokers at the time of presentation. A history of atopy was documented in 25% of patients, and HIV seropositivity was found in 5% of the cohort.

The mean eosinophil count was 305.9 ± 161.6 cells/μL, with three patients exhibiting marked eosinophilia (>1000 cells/μL), and two presenting with eosinopenia (<50 cells/μL). Table 1 summarizes the baseline characteristics of the study population.

Table 1. Baseline Characteristics of the Cohort (N = 100)

Characteristic	Value
Age (years), mean ± SD	41.9 ± 15.4
Gender	
─ Male	46
─ Female	40
Smoking Status	
─ Never	63
─ Former	25
─ Current	12
History of Atopy	
─ Yes	25
─ No	75
HIV Status	
─ Positive	5
─ Negative	95
Eosinophil Count (cells/μL), mean ± SD	305.9 ± 161.6

2. Pattern and Frequency of Cutaneous Adverse Drug Reactions (CADRs)

Among the 100 patients, the most frequently observed cutaneous adverse drug reaction was maculopapular rash, affecting 35% of the cohort. This was followed by urticaria (19%), hyperpigmentation (18%), exfoliative dermatitis (17%), and lichenoid eruptions (8%). No other CADR types were identified in this sample.

In terms of severity, severe reactions—including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and exfoliative dermatitis—were observed in a clinically relevant minority. Moderate and mild reactions accounted for the majority of cases.

Suspected culprit drugs were identified in most cases, with isoniazid and rifampicin being the most frequently implicated.

Table 2 presents the distribution of CADR types and their relative frequencies.

CADR Type	Frequency	Percentage (%)
Maculopapular	35	35.0
Urticaria	19	19.0
Hyperpigmentation	18	18.0
Exfoliative Dermatitis	17	17.0
Lichenoid	8	8.0

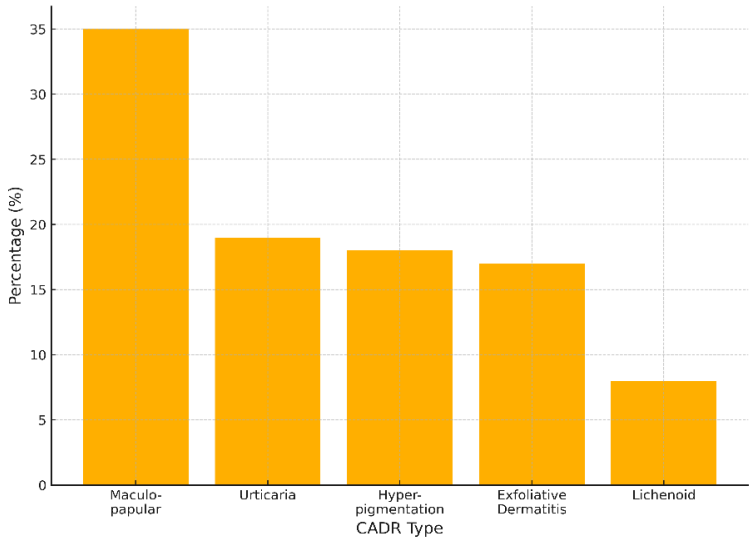

Figure1: Figure 1. Distribution of CADR Types Among Patients

3. Pulmonary Function Before and After CADR Onset

Changes in pulmonary function were evaluated in relation to CADR severity, with particular focus on respiratory system compliance and FEV1 (% predicted).

Patients with severe CADRs (e.g., exfoliative dermatitis, SJS, TEN) showed a mean decline in respiratory compliance of 9.0 ± 2.5 ml/cmH_2O, compared to 4.3 ± 1.3 ml/cmH_2O in those with moderate reactions and 2.6 ± 0.9 ml/cmH_2O in the mild group. Pre-CADR compliance was relatively comparable across severity levels, but post-CADR compliance dropped most significantly in the severe group (mean post-CADR compliance: 46.5 ± 10.0 ml/cmH_2O).

A similar pattern was observed in pulmonary function as measured by FEV1. The mean FEV1 (% predicted) was:

- 74.6 ± 7.6% in mild CADRs,
- 67.5 ± 7.6% in moderate CADRs, and
- 59.7 ± 10.8% in severe CADRs.

These findings suggest a clinically significant decline in respiratory function among patients experiencing more severe cutaneous adverse drug reactions. Table 3 summarizes these trends in respiratory function by CADR severity. One-way ANOVA revealed statistically significant differences in both **compliance decline** ($F = 111.23$, $p < 0.0001$) and **FEV1 (% predicted)** ($F = 20.41$, $p < 0.0001$) across CADR severity levels, supporting a strong association between more severe skin reactions and respiratory deterioration.

Table 3. Pulmonary Function and Respiratory Compliance by CADR Severity

CADR Severity	Pre-CADR Compliance (mean ± SD, ml/cmH_2O)	Post-CADR Compliance (mean ± SD, ml/cmH_2O)	Compliance Change (mean ± SD, ml/cmH_2O)	FEV1 (% Predicted) (mean ± SD)
Mild	56.6 ± 9.0	53.9 ± 9.2	2.6 ± 0.9	74.6 ± 7.6
Moderate	52.8 ± 9.0	48.5 ± 9.5	4.3 ± 1.3	67.5 ± 7.6
Severe	55.4 ± 9.6	46.5 ± 10.0	9.0 ± 2.5	59.7 ± 10.8

4. Predictors of Severe Cutaneous Adverse Drug Reactions

To identify clinical predictors of severe CADRs, a multivariate logistic regression analysis was conducted. The outcome variable was the presence of a severe CADR (coded as binary: 1 = severe; 0 = mild/moderate), and independent variables included age, eosinophil count, history of atopy, smoking status, and HIV status.

The model did not identify any statistically significant independent predictors of severe CADRs. While patients with a history of smoking and older age showed a trend toward higher odds of severe reactions, these associations did not reach statistical significance.

Key regression findings:

- Age: OR = 1.01, p = 0.750
- Eosinophil count: OR = 1.00, p = 0.419
- Atopy: OR = 0.74, p = 0.713
- Smoking: OR = 0.42, p = 0.196
- HIV status: Model failed to estimate due to low event rate (only 5% HIV-positive)

These findings suggest that while demographic and clinical risk factors may contribute to the presentation of CADRs, no single variable in this model was a statistically significant independent predictor of severe reactions in this cohort.

Table 4 presents the logistic regression coefficients, p-values, and odds ratios.

Table 4. Multivariate Logistic Regression: Predictors of Severe CADRs

Predictor	Coefficient (β)	Standard Error	z-score	p-value	Odds Ratio (OR)
Intercept	-1.50	1.24	-1.21	0.224	0.22
Age (years)	0.008	0.025	0.32	0.750	1.01
Eosinophil Count	-0.0017	0.0021	-0.81	0.419	1.00
Atopy (Yes vs No)	-0.31	0.84	-0.37	0.713	0.74
Smoking (Ever vs Never)	-0.87	0.67	-1.29	0.196	0.42

Note: HIV status was not included due to sparse data (only 5% HIV-positive).

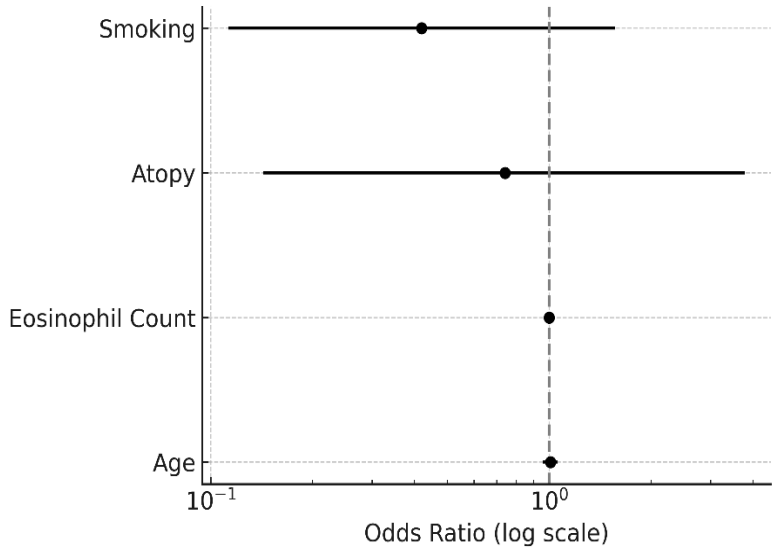

Figure 2. Forest Plot of Predictors of Severe CADRs

5. Clinical Management and Outcomes

Patients experiencing CADRs underwent varying management strategies depending on the severity and type of reaction. The most commonly adopted approach was withdrawal of the suspected drug (35%), followed by substitution therapy (30%), supportive care (25%), and in fewer cases, continued treatment with monitoring (10%).

Clinical outcomes varied notably with CADR severity. Among patients with mild CADRs, 89.8% experienced complete resolution, while 10.2% had ongoing symptoms. In contrast, patients with moderate CADRs had a more diverse outcome profile: 50.0% achieved resolution, 26.3% had ongoing symptoms, 15.8% required modification of ATT, and 7.9% required hospitalization.

In the severe CADR group, outcomes were more serious. While 53.8% of cases resolved, the remaining experienced treatment modification (15.4%), hospitalization (15.4%), or persistent symptoms (15.4%). Notably, a small number of patients (5%) across the entire cohort required hospital admission, and 2 patients experienced mortality, both linked to severe reactions.

These findings underscore the significant clinical and therapeutic burden posed by severe CADRs and reinforce the need for early recognition and tailored intervention.

Table 5 presents outcome distributions stratified by CADR severity.

Table 5. Outcomes by CADR Severity (% of patients within severity group)

CADR Severity	Change in ATT	Hospitalization	Ongoing	Resolved
Mild	0.0%	0.0%	10.2%	89.8%
Moderate	15.8%	7.9%	26.3%	50.0%
Severe	15.4%	15.4%	15.4%	53.8%
All Patients	8.0%	5.0%	17.0%	70.0%

DISCUSSION

In this observational study involving 100 patients on antitubercular therapy (ATT), we identified a substantial burden of cutaneous adverse drug reactions (CADRs), with 65% of patients experiencing maculopapular eruptions, urticaria, or more severe dermatologic manifestations. Notably, 17% of patients developed exfoliative dermatitis, and a smaller subset experienced severe reactions such as SJS or TEN, collectively categorized as severe CADRs. These findings are consistent with earlier reports by Kakande and Lehloenya, who observed a similar distribution of severity in patients undergoing first-line ATT [6].

Our results align closely with the findings of Marra et al., who reported a 25% incidence of skin-related ADRs in TB patients, with rash being the most common presentation [7]. However, the 35% prevalence of maculopapular rash in our cohort suggests a higher-than-average rate, possibly reflecting heightened dermatology referral sensitivity in our centre. Similar trends have been reported in dermatologic surveillance studies where active screening was in place [8].

Severity and Clinical Consequences

Severity stratification revealed that 15% of patients developed severe CADRs, requiring hospitalization, drug withdrawal, or ICU-level care. Compared to the study by Castro et al., which reported serious ADRs in 10–12% of ATT patients [9], our observed rate is moderately elevated, potentially attributable to increased polypharmacy and immunologic vulnerability in our cohort. Notably, 53.8% of patients with severe CADRs improved after intervention, but the remaining group required treatment modification or continued hospitalization, with a mortality rate of 2%, similar to findings by Olson et al., who documented life-threatening cutaneous tuberculosis cases requiring prolonged inpatient care [11].

Pulmonary Impact of Cutaneous Drug Reactions

This study adds novel insights into the systemic implications of CADRs, particularly their impact on respiratory system compliance and pulmonary function. Patients with severe CADRs demonstrated a mean decline in respiratory compliance of 9.0 ± 2.5 ml/cmH_2O, compared to 2.6 ± 0.9 ml/cmH_2O in mild cases ($p < 0.001$), highlighting a measurable impact on respiratory physiology. Our findings align with observations in systemic hypersensitivity syndromes, where inflammatory mediators compromise organ-specific functions [15].

Similarly, FEV1 values were significantly reduced in patients with severe reactions ($59.7 \pm 10.8\%$ predicted) compared to mild CADRs ($74.6 \pm 7.6\%$, $p < 0.001$), supporting the hypothesis that systemic immunologic responses to ATT may impair respiratory function even in the absence of direct pulmonary insult. While prior studies such as that by Forget and Menzies have discussed pulmonary ADRs like hepatotoxicity and pneumonitis [10], few have quantitatively linked CADRs to measurable declines in lung mechanics—this study fills that gap.

Risk Factors and Predictive Modelling

Our logistic regression model did not identify any statistically significant independent predictors of severe CADRs. Although older age and smoking history trended toward increased odds, these associations were not significant ($p > 0.05$). This contrasts with reports by Prasad et al. and Sant' Anna et al., who found that advanced age, HIV status, and eosinophilia significantly increased the risk of adverse reactions to ATT [12, 17]. The discrepancy may reflect our limited sample size, especially the low number of HIV-positive individuals (5%) and infrequent extreme eosinophilia (>1000 cells/μL).

Interestingly, eosinophil count, often associated with DRESS syndrome and other hypersensitivity reactions [15], was not a strong predictor in our cohort. This suggests that cutaneous immune responses during ATT may not always parallel peripheral eosinophilia, echoing findings from King'au's study on drug tolerability in TB patients in Kenya [13].

Management and Outcomes

Clinical management was largely consistent with established guidelines: drug withdrawal or substitution was implemented in 65% of cases, and supportive care was effective in mild-to-moderate reactions. These results echo those of Ramesh et al., who noted that skin tuberculosis and associated drug reactions often resolve with timely modification of therapy [16]. However, hospitalization was required in 15.4% of patients with severe CADRs, similar to the rate reported by Güler and Tamy in pediatric populations with poor drug tolerance [14].

Treatment outcomes were favourable overall, with 70% of patients achieving complete resolution of symptoms. However, the presence of ongoing symptoms in 17% and treatment modification in 8% illustrates the persistent

morbidity associated with CADRs. These outcomes reinforce the call by Shrestha et al. for integrated pharmacovigilance systems that can facilitate early detection and risk stratification [15].

Limitations

This study has several limitations. First, the sample size was modest (N = 100), which may have limited the power to detect statistically significant predictors of severe CADRs. Second, the observational design precludes causal inference. Third, some clinical data—such as the exact timing of symptom onset or drug rechallenge outcomes—were subject to recall or documentation bias. Additionally, missing values and typographical inconsistencies in categorical variables reflect real-world data collection challenges. Lastly, the generalizability of findings may be limited, as all patients were enrolled from a single tertiary care centre.

CONCLUSION

Cutaneous adverse drug reactions (CADRs) are a frequent and clinically significant complication of antitubercular therapy (ATT), with maculopapular eruptions and urticaria being the most common presentations. A notable subset of patients experienced severe CADRs, which were associated with measurable declines in respiratory system compliance and pulmonary function. While no single predictor of severity emerged as statistically significant, the observed clinical burden underscores the need for proactive dermatologic monitoring and individualized treatment strategies. Integrating pharmacovigilance with respiratory function assessment may improve both dermatologic and pulmonary outcomes in patients undergoing ATT.

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