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Original Research Article

Comparative Profile of Adverse Drug Reactions in Drug-Sensitive and Drug-Resistant Tuberculosis Patients Receiving ATT under NTEP: A Prospective Observational Study

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Conflict of interest: Nil

Abstract

Background: In India, tuberculosis (TB) is still a significant public health issue. Adverse drug reactions (ADRs) during treatment with antitubercular therapy (ATT), tend to lead to poor adherence to treatment and negative treatment outcomes. Patients with drug resistant tuberculosis (DR-TB) who are on extensive second-line regimens are especially at risk for serious ADRs. There is a lack of data on the differences in ADR profiles between patients with drug-sensitive TB (DS-TB) and DR-TB under programming conditions in India. This study aimed to assess and compare the ADR profiles of both DS-TB and DR-TB patients receiving ATT under the National Tuberculosis Elimination Programme (NTEP).

Methods: From January 2023 to January 2025, a prospective study of tuberculosis (TB) patients on anti-TB therapy was conducted at a tertiary level care medical school hospital located in Gujarat, India. The study consisted of 100 TB patients (50 DS-TB; 50 DR-TB) who received treatment in the outpatient department (OPD) of the hospital. Baseline demographic and clinical data were captured at the beginning of the treatment period, along with a record of any adverse drug reactions (ADRs) that occurred during that time. Health records were monitored for the occurrence of ADRs throughout the entire treatment period. Causality was assessed using the WHO-Uppsala Monitoring Centre (WHO-UMC) causality assessment scale, and severity was assessed using the modified Hartwig and Siegel severity assessment scale. Chi-square ($\chi 2$) and Fisher's exact tests were used to perform statistical analyses of the data. A p-value of 0.05 was used to determine statistical significance.

Results: One hundred patient participants had 148 AD events recorded in their medical records. GI AD events were seen at the highest frequency (35.1%); however, there were also many hepatobiliary (18.2%) and neurologic (16.2%) reports too. Compared to DS-TB patients, DR-TB patients had higher rates of peripheral neuropathy (36.4% vs. 6.4%, $p < 0.001$), psych manifestations (18.2% vs. 1.3%, $p = 0.002$), arthralgia/myalgia (27.3% vs. 11.5%, $p = 0.048$), ototoxicity (9.1% vs. 0%, $p = 0.009$), and QT interval prolongation (9.1% vs. 0%, $p = 0.009$). As well, most AD events (91.9%) were of mild to moderate intensity. Per WHO-UMC guidelines, most AD events are determined to have a probable relationship. 50% of AD events were treated symptomatically only; 19.6% of AD events required temporary suspension of the drug causing the AD event.

Conclusion: Patients with tuberculosis (TB) on antitubercular therapy (ATT) through the national tuberculosis elimination program (NTEP) are at risk for experiencing adverse drug reactions (ADRs). Drug-resistant TB patients treated with second-line drugs are especially at risk of developing neuropsychiatric and cardiotoxic ADRs. Early identification of ADRs, active methods of monitoring side effects, and prompt treatment of ADRs will improve adherence to treatment and improve the overall outcome of treatment for DR-TB patients.

Keywords: Tuberculosis; Adverse Drug Reactions; Drug-Resistant Tuberculosis; Drug-Sensitive Tuberculosis; Antitubercular Therapy; Pharmacovigilance; NTEP.

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Introduction

Even though effective chemotherapy exists to treat Tuberculosis (TB), it still ranks as one of the top infectious diseases in the world that causes people to be sick or die. The World Health Organization (WHO) Global Tuberculosis Report 2024 reported that in 2023 an estimated 10.8 million people developed TB around the world and 1.25 million people died from it. Nearly a quarter of the world's TB burden originates in India, making TB elimination a significant public health concern in this country. [1]

NTEP has greatly enhanced the TB program in India by instituting universal DST, a unified treatment protocol, electronic surveillance system, and pharmacovigilance for drugs. Despite these interventions, ATT is still associated with many adverse drug reactions that pose serious problems during treatment and adherence to ATT drugs. Consequently, there is a need to develop novel therapeutic approaches for ATT-resistant tuberculosis. [1]

An adverse drug reaction (ADR), according to the definition of the WHO, "is any response to a drug which is noxious and unintended and which occurs at doses normally used in humans." ADRs are significant factors in causing morbidity, hospitalization, treatment discontinuation, and added health care costs. [2]

Antitubercular treatment requires long-term combination therapy with a high prevalence of adverse effects. Antitubercular first-line medications like isoniazid, rifampicin, pyrazinamide, and ethambutol are recognized for causing hepatotoxicity, nausea, skin reactions, peripheral neuropathy, and optic neuritis. However, antitubercular adverse events become more prevalent when treating drug-resistant TB, which requires long-term exposure to second-line antitubercular medications like fluoroquinolones, linezolid, bedaquiline, and injectables, leading to severe ADRs like cardiotoxicity, neurotoxicity, nephrotoxicity. [1]

DS-TB is usually responsive to the conventional treatment regimen while DR-TB demands more complicated regimens which are not only lengthy but also involve greater number of tablets and lower tolerance. There is sufficient evidence suggesting that drug side effects occur more commonly in DR-TB cases, leading to discontinuation of therapy, poor compliance, default and development of additional resistance. Such problems have an adverse impact on treatment effectiveness and create a major barrier to the eradication of the disease. [1]

The risk of ADRs is determined by numerous patient-related and medication-related variables such as the age of the patient, malnutrition, co-morbidities, HIV status, diabetes mellitus, alcohol abuse, previous exposure to ATT, and genetic polymorphisms that influence drug metabolism. Moreover, the time duration of the therapy and the distribution of the drugs in cases of pulmonary and extrapulmonary tuberculosis can vary, leading to altered ADR patterns. The early diagnosis and appropriate management of ADRs are hence vital in ensuring adherence to the ATT regimen. [3]

Pharmacovigilance has become an essential part of TB treatment using NTEP. The Nikshay program and other drug safety surveillance systems seek to ensure better identification and reporting of ADRs, especially among DR-TB patients who are on novel antitubercular drugs. Yet, ADRs have continued to be underreported in practice, especially in low-resource areas, and there are few studies from India comparing ADR occurrence between DS-TB and DR-TB patients. [1,4]

The understanding of the comparative range of ADRs between drug-sensitive and drug-resistant cases is significant in the formulation of effective strategies of treatment. It will help minimize disruptions in treatment schedules as well as enhance efficacy in overall treatment. The current study was hence carried out to compare ADRs in both drug-sensitive and drug-resistant cases of TB undergoing antitubercular treatment within the framework of NTEP.

Methodology

Study Design and Setting: An observational prospective study was done in the department of Respiratory medicine of GMERS medical college and civil hospital, Sola, Ahmedabad, and Gujarat, India. The study was done within a period of two years from January 2023 to January 2025. The institute operates as a tertiary care teaching hospital under the National Tuberculosis Elimination Program (NTEP) and acts as a referral center for patients with both DS-TB and DR-TB.

The study design was to compare the adverse drug reactions (ADR) profile in patients undergoing antitubercular therapy (ATT). Patients were followed up on a prospective basis since ATT

treatment started until the end of their ATT treatment duration.

Study Population: The study population consisted of adult patients with pulmonary or extrapulmonary TB undergoing ATT according to NTEP guidelines within the study duration.

The patients were classified as follows:

- DS-TB
- DR-TB

Depending upon the results of their microbiology and DST reports under NTEP guidelines.

Inclusion Criteria

- Patients aged ≥18 years.
- Confirmed cases of pulmonary or extrapulmonary tuberculosis by clinical, radiographic, microbiological, or histopathologic examination.
- Patients undergoing treatment with either first- or second-line ATT under NTEP.
- Patients who agree to participate and sign an informed consent form.

Exclusion Criteria

- Patients younger than 18 years.
- Patients who declined consent to participate in the study.
- Patients with insufficient clinical records or follow-up data.
- Patients receiving ATT therapy from other hospitals within sufficient baseline information.

Number of Participants and Sample Strategy: A sample size of 100 patients that met the inclusion criteria was selected throughout the study period by using convenient sampling. Patients meeting the inclusion criteria who attended the outpatient department or those admitted to the inpatient department during the study period were recruited.

Both new and old patients of TB were included in the study.

Criteria for Diagnosis: Tuberculosis was diagnosed based on NTEP guidelines using any one of the following:

- A smear microscopy for acid-fast bacilli (AFB)
- CBNAAT
- LPA
- DST using culture
- Chest radiograph and HRCT thorax
- Histopathology or fluid examination in extra-pulmonary tuberculosis

Resistance to drugs was determined by CBNAAT, LPA, or DST using culture.

Procedure for Data Collection: Patients who qualified for the study were recruited after securing their signed consent to participate. The demographic, clinical, laboratory, and treatment-related data were captured on a pre-designed proforma.

The following data were captured:

- Age, gender, body weight, and location of residency
- Smoking and alcohol consumption history
- Past history of ATT
- Any other diseases like diabetes mellitus, hypertension, HIV, thyroid disorder, liver, and kidney conditions
- Site and type of TB
- Drug susceptibility profile
- Details of the ATT regime

Clinical assessment was carried out at baseline and follow-up visits. Laboratory tests were done as per the NTEP guidelines. Baseline and Follow-up Investigations

The following investigations were performed:

- Complete blood count (CBC)
- Liver function tests (LFT)
- Renal function tests (RFT)
- Random blood sugar (RBS)
- Serum uric acid
- Serum electrolytes including magnesium
- Thyroid function tests where indicated
- HIV testing after counseling and consent
- Electrocardiography (ECG) in DR-TB patients receiving bedaquiline-containing regimens
- Audiometry where injectable agents were used
- Ophthalmological evaluation in patients receiving ethambutol or linezolid

Additional investigations were performed based on clinical presentation and suspected ADRs.

Adverse Drug Reaction Definition and Evaluation: A definition of adverse drug reaction based on that of WHO was used: "any noxious, unintended, and undesired effect of a drug occurring at commonly used doses."

All cases of adverse drug reactions observed after the introduction of ATT were recorded and analyzed.

The parameters of adverse drug reactions were as follows:

- Time of onset of the reaction
- Clinical manifestation
- Drug suspected as an agent causing the adverse reaction
- Body system involved
- Seriousness of the reaction
- Management of the adverse reaction

Assessment of Causality: The WHO-Uppsala Monitoring Centre (WHO-UMC) causality

assessment scale was used in assessing the causality of adverse drug reactions. Adverse drug reactions were classified as:

- Certain
- Probable
- Possible
- Unlikely

Assessment of Severity

The severity of the ADRs was rated on the modified Hartwig and Siegel severity assessment scale as follows:

- Mild
- Moderate
- Severe

The mild ADRs needed little or no treatment, moderate ADRs needed treatment change or other treatments, while severe ADRs led to hospitalization, life-threatening conditions, or disabilities.

Management of ADRs: Management of ADRs was done in accordance with NTEP and institutional treatment guidelines. Based on the severity of the problem, management measures included:

- Symptomatic management
- Adjusting dose
- Drug holiday
- Drug substitution
- Permanent withdrawal of causative drugs

Outcome Indicators

Primary Outcome Indicator

- Comparing the nature and incidence of adverse drug reactions in DS-TB and DR-TB subjects under ATT.

Secondary Outcome Indicators

- Evaluating the seriousness and organ involvement in adverse drug reactions.
- Evaluating the approaches used to manage adverse drug reactions.
- Evaluating changes made to treatment based on adverse drug reactions.
- Evaluating clinical determinants linked with adverse drug reactions.

Ethical Issues: The study was approved by the Institutional Ethics Committee, GMERS Medical College and Civil Hospital, Sola, Ahmedabad.

Informed consent was taken in writing from each individual before recruitment. All information related to the patients remained confidential during the study. The study followed ethical issues described in the Declaration of Helsinki.

Statistical Analysis: The data were collected on Microsoft Excel software and analyzed on SPSS software version 26.0.

Continuous variables were represented as mean±standard deviation (SD) or median with interquartile range (IQR). Categorical variables were represented as frequency and percentage.

Differences between DS-TB group and DR-TB group were evaluated by

- Chi-square test or Fisher's exact test for categorical variables
- Student's t-test or Mann Whitney u-test for continuous variables

Statistical significance was defined as $P<0.05$.

Results

Study Population: A total of 100 tuberculosis patients receiving antitubercular therapy (ATT) under the National Tuberculosis Elimination Programme (NTEP) were included in the study. Patients were categorized into drug-sensitive tuberculosis (DS-TB) and drug-resistant tuberculosis (DR-TB) groups based on drug susceptibility testing. Both pulmonary tuberculosis (PTB) and extrapulmonary tuberculosis (EPTB) cases were included. Among the study participants, 78% had drug-sensitive TB while 22% had drug-resistant TB. Pulmonary TB constituted the majority of cases (67%), whereas 33% patients had extrapulmonary involvement.

Table 1: Baseline demographic and clinical characteristics of study participants (N = 100)

Variable	Category	Frequency (%)
Age group (years)	18–30	32 (32.0)
	31–45	41 (41.0)
	46–60	20 (20.0)
	>60	7 (7.0)
Gender	Male	64 (64.0)
	Female	36 (36.0)
Tuberculosis type	Pulmonary TB	67 (67.0)
	Extrapulmonary TB	33 (33.0)
Drug sensitivity status	Drug-sensitive TB	78 (78.0)
	Drug-resistant TB	22 (22.0)
Previous ATT history	Present	28 (28.0)
	Absent	72 (72.0)

Comorbidity	Present	31 (31.0)
	Absent	69 (69.0)

The majority of study participants belonged to the 31–45 years age group with male predominance.

Nearly one-third of patients had associated comorbidities, while 28% had previous exposure to ATT. A total of 148 adverse drug reactions (ADRs) were documented among 100 study participants during the study period. Gastrointestinal adverse effects were the most common ADRs observed, followed by hepatobiliary, neurological, musculoskeletal, dermatological, and ophthalmological reactions.

Table 2: Overall organ system-wise distribution and severity grading of adverse drug reactions (N = 148)

Variable	Frequency (%)
Organ system involved	
Gastrointestinal	52 (35.1)
Hepatobiliary	27 (18.2)
Neurological	24 (16.2)
Musculoskeletal	18 (12.2)
Dermatological	14 (9.5)
Ophthalmological	7 (4.7)
Renal	4 (2.7)
Cardiac	2 (1.4)
Severity grading	
Mild	88 (59.5)
Moderate	48 (32.4)
Severe	12 (8.1)

Gastrointestinal intolerance including nausea, vomiting, gastritis, and abdominal discomfort represented the largest proportion of ADRs. Most ADRs were mild to moderate in severity and were managed conservatively.

Table 3: Comparative profile of adverse drug reactions between DS-TB and DR-TB patients

Adverse drug reaction	DS-TB (n=78)	DR-TB (n=22)	p-value
Gastrointestinal reactions	32 (41.0)	11 (50.0)	0.452
Hepatotoxicity	18 (23.1)	4 (18.2)	0.621
Peripheral neuropathy	5 (6.4)	8 (36.4)	<0.001*
Psychiatric symptoms	1 (1.3)	4 (18.2)	0.002*
Arthralgia/myalgia	9 (11.5)	6 (27.3)	0.048*
Dermatological reactions	8 (10.3)	3 (13.6)	0.658
Ototoxicity	0 (0.0)	2 (9.1)	0.009*
QT prolongation	0 (0.0)	2 (9.1)	0.009*

***Statistically significant, *** F test is used**

Drug-resistant TB patients experienced significantly higher rates of neurotoxicity, psychiatric manifestations, musculoskeletal ADRs, ototoxicity, and QT prolongation compared to drug-sensitive TB patients.

Table 4: Causality assessment and management of adverse drug reactions

Variable	Frequency (%)
WHO-UMC causality assessment	
Certain	12 (8.1)
Probable	79 (53.4)
Possible	53 (35.8)
Unlikely	4 (2.7)
Management strategy adopted	
Symptomatic treatment only	74 (50.0)
Dose modification	21 (14.2)
Temporary drug interruption	29 (19.6)
Drug substitution	18 (12.2)
Permanent discontinuation	6 (4.0)

The majority of ADRs were categorized as probable according to WHO-UMC causality assessment criteria. Most ADRs were managed successfully with symptomatic treatment and temporary treatment modification.

Table 5: Impact of ADRs on treatment continuation and clinical outcome

Variable	Frequency (%)
No treatment interruption	69 (69.0)
Temporary interruption of ATT	25 (25.0)
Permanent regimen modification	6 (6.0)
Recovery after ADR management	89 (89.0)
Ongoing treatment at follow-up	8 (8.0)
Severe persistent toxicity	3 (3.0)

Although ADRs were common, the majority of patients were able to continue ATT with appropriate monitoring and management.

According to the findings of the current study, patients with tuberculosis receiving ATT as part of the NTEP program experienced a substantial number of adverse drug reactions. The gastrointestinal tract and hepatobiliary system were most frequently affected by the ADRs of the medications. Drug resistant TB had a greater rate of neurotoxic, psychiatric, muscular and cardiotoxic ADRs compared to those who are drug sensitive. Most of the ADRs were classified as low and moderate severity; all patients were able to successfully treat their ADRs with dose reduction or a temporary stop in therapy.

Discussion

The current study was a prospective observational research project designed to assess the incidence of adverse drug reactions (ADRs) experienced by patients with drug-sensitive tuberculosis (DS-TB) and drug-resistant tuberculosis (DR-TB), and compare them to each other while on anti-tubercular therapy (ATT) as specified by the National Tuberculosis Elimination Programme (NTEP). A total of 148 ADRs were identified amongst the 100 participants included in this study, emphasising the large amount of medication-related toxicity associated with treatment of TB.

Most of the patients in this study were 31 to 45 years old and were predominately male, which is consistent with the findings from many other studies performed within India on ADRs in TB patients. For instance, Hire et al. have found that men are the most affected demographic in MDR-TB cases in Central India due to greater occupational exposure, smoking, alcohol use, and poor health-seeking behaviour relative to women. [5]

The majority of adverse drug reactions (ADRs) identified in the current research study were gastrointestinal in origin, as 35.1% of the total reported ADRs were categorized as gastrointestinal. Patients taking first line ATT for DS-TB frequently experienced nausea/vomiting, gastritis or abdominal discomfort. Further research conducted previously through pharmacovigilance studies in India has also demonstrated that gastrointestinal intolerance is by far the most common ADR associated with regimens containing rifampicin and/or pyrazinamide. [6-8]

The current study demonstrated that hepatotoxicity was one of the key adverse drug reactions (ADRs). The proportion of individuals developing hepatotoxicity among DS TB individuals was 23.1%, which was similar to levels seen in previous studies evaluating the impact of first-line anti-tuberculosis therapy on hepatic function. Hepatic injury caused by isoniazid, rifampicin and pyrazinamide remains one of the most clinically relevant ADRs because in most cases; the ADRs require that the course of therapy be interrupted temporarily (due to the possibility of on-going liver damage) and increase the likelihood of patients not adhering to their TB therapy regimen. Edwards and Aronson noted that ADRs causing hepatotoxicity are a primary contributor to treatment related morbidity and hospitalization worldwide. [3]

An essential finding of this study was that there were significantly increased rates of neurological/psychiatric adverse drug reactions among patients with drug-resistant tuberculosis (DR-TB) compared to those with drug-sensitive tuberculosis (DS-TB). Peripheral neuropathy occurred in 36.4% of patients with DR-TB as compared to others that were treated for drug sensitive TB (DS-TB) ($p<0.001$). This finding is similar to that seen in other studies in India assessing linezolid-based treatment regimens for DR-TB. In another study attributed by Mishra et al. on the adverse drug reactions associated with linezolid therapy about 42% of patients receiving treatment for multidrug-resistant (MDR-TB) or rifampicin-resistant TB (RR-TB) developed peripheral neuropathy; furthering treatment alteration would be on the basis of peripheral neuropathy. [9]

Vijay Kumar et al. similarly found that the main reason for changing therapies among patients on an all-oral long duration of treatment regimen for multidrug-resistant tuberculosis was peripheral neuropathy. The authors also found that thrombocytopenia, optic neuritis, and skin pigmentation occurred at high rates as a result of long-term use of second-line agents. [10]

Psychiatric symptoms consistent with DR-TB (depression, anxiety & mood swings) were

significantly more common among our study population compared to those of the national & international control groups. Cycloserine-based regimens have been found to produce neuropsychiatric toxicities after extended period of time on these therapies. Similar outcomes were reported from pharmacovigilance studies performed in the context of the PMDT programme in India. [6]

In this study, DR-TB patients only demonstrated evidence of ototoxicity and QT prolongation as AEs. Despite their low frequency, these are serious AEs; can be permanent and/or may cause fatal complications such as heart failure or hearing loss. The potential for QT prolongation due to Bedaquiline treatment and ototoxicity due to injection treatment have both been more frequently noted in recent DR-TB treatment programs. Therefore, on-going ECG and audiogram monitoring remains a necessary component of active drug safety monitoring for NTEP purposes. [9,10]

The majority of ADRs reported in the present study were classified as mild to moderate, with only 8.1% being classified as severe. In a similar study, Baig et al found that most MDR-TB ADRs could be managed with adequate intervention and proper monitoring. [7] The relatively low number of severe adverse drug reactions (ADRs) reported in this study may be due to the early identification and treatment of patients seen at a tertiary care center through continued patient follow-up.

Most of the ADRs reported in this study were determined to be probable using the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) causality assessment system. Similar results have been observed with other studies that have examined ADRs associated with second-line anti-tuberculosis drug (ATT) regimens in India. [5,7] Using standardized tools to assess causality helps ensure that ADR reports are more reliable and enhance the quality of pharmacovigilance.

Under half the ADR cases experienced Symptomatic Treatment alone while a Temporary Drug Interruption & Regimen Modification was enough for some patients. The ability of patients to continue ATT after receiving appropriate Management is very important to the early detection of ADR and taking a multidisciplinary approach in the management of patients will help reduce treatment defaulters and improve adherence to treatment. DR-TB's increasing burden in India highlights the need for strong ADR monitoring programs. A recent systematic review conducted in India found that the rates of drug resistance remain significantly higher among previously-treated patients. Assuch, there is an increased necessity to develop treatment regimens that are safer and have fewer adverse effects. [11]'The results of recent changes to the NTEP to incorporate shorter, all-oral regimens have shown positive improvements in treatment outcomes and reduced long-term toxicity. [12] The conclusions from this study have important implications for both clinical and public health; therefore, the following key activities must take place to ensure successful treatment of tuberculosis, especially for those DR-TB patients receiving lengthy multi-drug regimens: active pharmacovigilance, routine patient education, timely laboratory monitoring, and quick intervention when an adverse event occurs. Increasing surveillance of ADR's under the NTEP may improve treatment compliance, decrease morbidity, and help achieve the national TB elimination goal.

This study had several advantages, one of which was that it was designed around observing prospective participants actively monitored for AIDS-related discomfort (ADR) in "real-world" programmatic settings. Another advantage was that it compared the toxicity between patients receiving first-line and second-line ATT, as well as between those on DS-TB and DR-TB.

While the comparison between the DS and DR patients has allowed for valuable information describing the differences in terms of the toxicity of first- and second-line ATT regimens, due to the study being conducted at only one tertiary care center, and the study sample being small, the results may not be generalizable. Continued long-term, multicentric studies with larger sample sizes are needed to continue to evaluate the safety profiles of newer antitubercular regimens.

Conclusion

This research has revealed a high incidence of adverse drug reactions (ADRs) in patients who are receiving antitubercular therapy for their tuberculosis disease. ADRs occurred to a lesser degree at a rate of 35.1%, followed by 18.2% and 16.2% respectively for the gastrointestinal, hepatobiliary, and neurological systems.

Among patients who have drug-resistant tuberculosis (DR-TB), there was a significantly higher incidence of peripheral neuropathy (36.4% vs 6.4%) and psychiatric manifestations (18.2% vs 1.3%), as well as ototoxicity (9.1% vs 0%) and QT prolongation (9.1% vs 0%) when compared to those who were drug sensitive (DS-TB).

The majority of ADRs were of mild to moderate severity, and the majority of patients continued to receive their antitubercular therapy successfully with symptomatic management or temporary modification of their treatment.

The findings of this study emphasize the importance of ongoing pharmacovigilance, early identification and treatment of ADRs, and regular monitoring throughout the course of antitubercular therapy, especially for patients with DR-TB who are receiving extended second-line therapy under the NTEP program.

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Ethical consideration: This study was approved by the Institutional Ethics Committee of GMERS Medical College and Civil Hospital, Sola, Ahmedabad. The research was performed according to the ethical standards established by the Declaration of Helsinki.

Informed Consent: Informed consent was obtained prior to including any subject in the study.

Author Contributions: All authors made significant contributions towards the design and conception of the study, data collection, analyses, interpretation of the data, drafting the manuscript, revising it critically for important intellectual content and giving final approval of the version published.

Data Availability Statement: The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

AI Declaration: Artificial intelligence-assisted tools were used only for language refinement, grammatical correction, and improvement of manuscript readability.

All scientific content, study design, data analysis, interpretation, and final manuscript approval were performed solely by the authors. The authors take full responsibility for the accuracy, originality, and integrity of the work presented in this manuscript.

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