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Evaluating The Safety Profile Of Nintedanib Among ILD Patients In A Tertiary Care Hospital: A Prospective Research Approach Focusing On Adverse Drug Reactions

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Abstract
Background: *Nintedanib, a multi-target tyrosine kinase inhibitor, slows progression of fibrotic interstitial lung diseases (ILDs) but is frequently complicated by adverse drug reactions (ADRs). This prospective observational study evaluated the incidence, predictors, and management of Nintedanib-associated ADRs in an Indian tertiary-care cohort.*
Methods: *Thirty patients with fibrotic ILD received Nintedanib 150 mg twice daily and were followed over six months. Demographic, clinical data were collected. ADRs were coded by type and severity; causality was assessed using the WHO-UMC scale. Associations between patient characteristics and key ADRs (notably diarrhea) were examined via chi-square tests and independent t-tests. Logistic regression identified independent predictors of dose modification. Spearman's correlation assessed the relationship between total ADR burden and treatment duration.*
Results: *A total of 143 ADRs (mean 4.8 per patient) were recorded. Fatigue (70.0%) and diarrhea (60.0%) were most common; liver-function abnormalities occurred in 56.7%. Female sex (66.7% vs. 11.1%, $p = 0.006$) and advanced age (68.5 vs. 60.5 years, $p = 0.017$) were significantly associated with diarrhea development. Diarrhea emerged as the strongest predictor of dose modification ($\beta = 2.50$, $p < 0.001$). Sixty percent of patients required dose reduction or temporary interruption; Spearman's $\rho = -0.335$ ($p = 0.071$) indicated a trend toward shorter treatment duration with higher ADR burden. WHO-UMC causality assessment classified 55.5% of diarrhea cases as "Certain" or "Probable."*
Conclusion: *In this real-world Indian cohort, Nintedanib therapy incurred a high ADR burden, particularly gastrointestinal toxicity in older and female patients, leading to frequent dose adjustments. Most ADRs were manageable through supportive care and patient education, enabling continued treatment. These findings underscore the need for proactive monitoring and individualized management strategies, and they provide novel region-specific pharmacovigilance data to inform global ILD care.*
Key words: *Interstitial lung disease, tyrosine kinase inhibitor, nintedanib, respiratory disorder, ADR monitoring*

INTRODUCTION

Adverse drug reactions (ADRs), According to WHO as toxic, undesirable responses at normal therapeutic doses, drive morbidity, longer hospital stays, and higher healthcare costs. According to the Rawlins–Thompson classification, ADRs are: Type A (augmented, expected), Type B (peculiar response), Type C (long term reaction), Type D (late reaction), Type E (withdrawal), and Type F (therapeutic failure) [1]. Fibrotic interstitial lung diseases feature progressive lung scarring and high risk of death. Nintedanib, a multitarget tyrosine kinase inhibitor, slows lung function decline but often causes gastrointestinal ADRs—especially diarrhea and nausea—that can impair adherence. This study aims to quantify Nintedanib ADR incidence in fibrotic ILD, identify high-risk patient characteristics, evaluate effects on adherence and outcomes, and explore tolerability-enhancing strategies [2].

Interstitial Lung Disease and Nintedanib: Overview

Interstitial lung diseases (ILDs) comprise a heterogeneous collection of more than 200 lung disorders, marked by persistent inflammation and progressive scarring of the lung interstitial, alveoli, bronchioles, and capillary endothelium. ILD subtypes include idiopathic interstitial pneumonias (e.g., IPF, NSIP, COP), connective tissue disease-associated ILDs, granulomatous types (e.g., sarcoidosis, hypersensitivity pneumonitis), and exposure-related forms such as occupational and drug-induced ILDs. In India, the ILD spectrum shows higher prevalence of hypersensitivity pneumonitis linked to biomass fuel exposure, with challenges including delayed diagnosis, limited specialist access, and financial constraints impacting antifibrotic treatment. Globally, IPF affects about 13–20 per 100,000, mainly in those over 60 years [3].

Nintedanib is an orally administered small-molecule tyrosine kinase inhibitor that slows fibrotic ILD progression by competitively inhibiting ATP-binding domains of key receptor tyrosine kinases involved in fibrosis and angiogenesis including PDGFR-α/β, FGFR-1/2/3, and VEGFR-1/2/3.This multi-target inhibition disrupts profibrotic signalling pathways, reducing fibroblast activation and extracellular matrix deposition [4].

Adverse Drug Reaction Profile of Nintedanib

Gastrointestinal ADRs: Diarrhea (50-75%), Nausea/Vomiting (20-40%), Weight Loss (10-20%)
Hepatic ADRs: Liver enzyme elevations (4 per 1000 patient-years), rare hepatotoxicity
Cardiovascular/bleeding: Bleeding (24.2 per 1000 patient-years), MI & Stroke (3.3 per 1000 patient-years)
Serious ADRs: Gastrointestinal perforation (0.9 per 1000 patient-years)
Other ADRs: Skin ulcers, infections, decreased appetite, fatigue (10-20%)

METHODOLOGY

Research Design and Setting

This prospective observational investigation, carried out from December 2024 to May 2025 at the IPD of Pulmonary Department, Shri Mahant Indresh Hospital, Dehradun and assessed the incidences, profile, and impact of Nintedanib-related adverse drug reactions in patients with fibrotic interstitial lung disease using detailed inpatient and discharge record reviews.

Inclusion Criteria:

- Diagnosed with fibrotic interstitial lung disease
- Receiving Nintedanib treatment
- Age ≥ 18 years
- Provided informed consent

Exclusion Criteria:

- Incomplete medical records
- Concurrent use of other antifibrotic medications
- History of Nintedanib intolerance

Participants

Participants with complete clinical data & demographic data were included, while those discontinuing for non-clinical reasons, lost to follow-up, or with incomplete/unclear records were excluded. Thirty patients met these criteria. The Institutional Ethics Committee granted approval for this study (IEC Reg. No. ECR/710/Inst/UK/2015/RR-21; Reference: SGRR/IEC/29/24).

Outcome Measures

The main objective was to assess the incidence and characteristics of Nintedanib-related ADRs, focusing on gastrointestinal (diarrhea, nausea, vomiting, abdominal pain), constitutional (fatigue, headache), respiratory symptoms, and laboratory abnormalities (LFT, KFT, CBC). Secondary outcomes included associations between patient demographics (age, sex, weight) and ADRs, the effect of ADRs on adherence (dose adjustments/interruptions), and WHO causality classification as definite, probable, possible, or unlikely.

Statistical Analysis

Data were compiled in Microsoft Excel and analysed in RStudio (v4.5). Chi-square tests examined relationship between categorical variables (e.g., sex and ADRs), *t*-tests compared continuous variables (e.g., age across ADR subgroups), and logistic regression identified predictors of dose adjustments (age, sex, key ADRs). Spearman's correlation evaluated the link between ADR burden and treatment duration. Visualizations (bar charts, scatter plots, boxplots) were created using *ggplot2* and *ggpubr*. Statistical significance was set at $p<0.05$.

RESULTS

Participant Demographics and Baseline Data

30 Participants (mean age 60.0 ± 8.4 years; 60% male) with fibrotic ILD on Nintedanib were evaluated. Mean BMI was 24.8 ± 4.0 kg/m^2; disease duration averaged 25.1 ± 12.0 months. Baseline FVC and DLCO were 77.7 ± 9.8% and 58.5 ± 10.9% predicted, respectively. Urban residents comprised 53%, graduates 47%, and homemakers 30%. Middle-, low-, and high-income groups accounted for 47%, 37%,

and 17%. Non-smokers were 60%; smokers/ex-smokers 40%. Half consumed alcohol. Comorbidities included CAD (17%), COPD and diabetes (each 13%), hypertension (10%), and none (33%) [5].

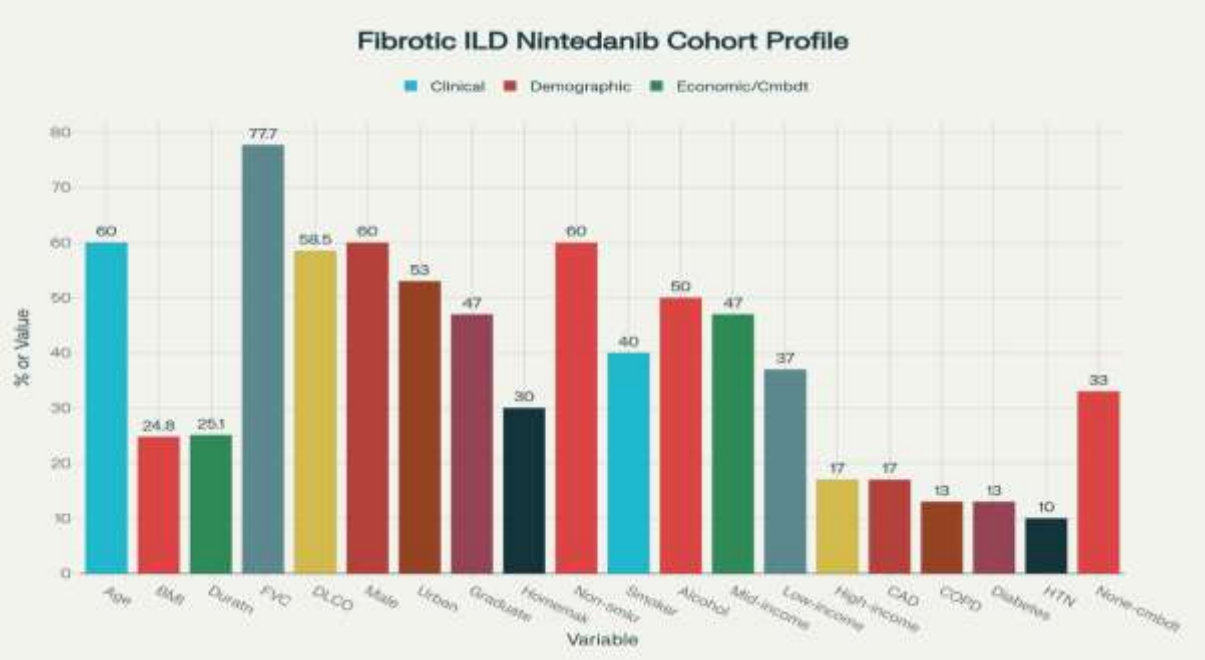

Fig 1: Patient Baseline Data in Fibrotic ILD Undergoing Nintedanib Therapy

Adverse Drug Reaction Incidence and Pattern

During the observation period of this study involving 30 Participants with fibrotic interstitial lung disease managed with Nintedanib, a total of 143 adverse drug reactions (ADRs) were documented, averaging 4.77 ADRs per patient. The most seen ADR was fatigue, reported by 70% of patients, followed by diarrhea and headache at 60% each. Other frequent symptoms included chest pain and cough (both 56.7%), shortness of breath (50%), abdominal pain and nausea/vomiting (each 43.3%), and wheezing (36.7%) [6].

Laboratory abnormalities were also notable, with liver function test (LFT) abnormalities observed in 56.7% of patients, kidney function test (KFT) abnormalities in 50%, and complete blood count (CBC) abnormalities in 43.3%. These results underscore the multi-systemic impact of Nintedanib therapy and highlight the necessity for comprehensive clinical and laboratory monitoring during treatment [7][8].

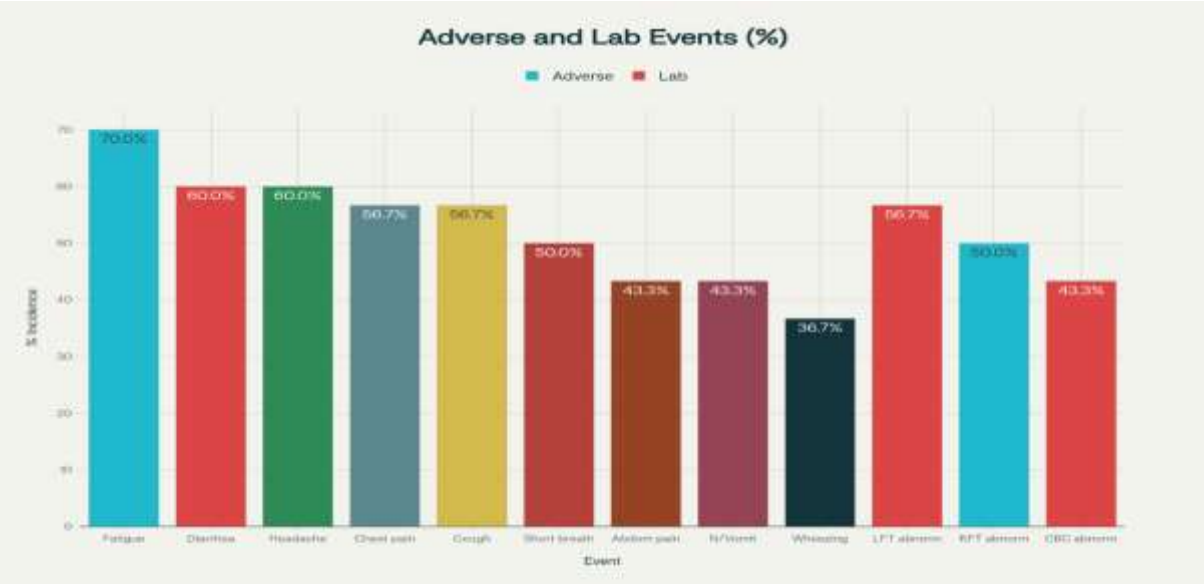

Fig: 2 Frequencies of Adverse Drug Reactions and Laboratory Abnormalities in Patients Receiving Nintedanib

Risk Factor Analysis for Adverse Drug Reactions

Statistical analysis showed significant demographic and clinical associations with adverse drug reactions during Nintedanib therapy in fibrotic ILD. Females had a notably higher prevalence of diarrhea (66.7%) compared to males (11.1%) ($\chi^2 = 7.656$, $p = 0.006$). Age was also a significant factor; patients experiencing diarrhea were older on average (68.5 years) than those without diarrhea (60.5 years) ($t = -2.57$, $p = 0.017$). In multivariate logistic regression evaluating predictors of dose adjustment, diarrhea was the strongest independent predictor ($\beta = 2.5$, $p < 0.001$), followed by fatigue ($\beta = 0.8$, $p = 0.050$). Age and female sex showed trends but were not statistically significant in this model [9].

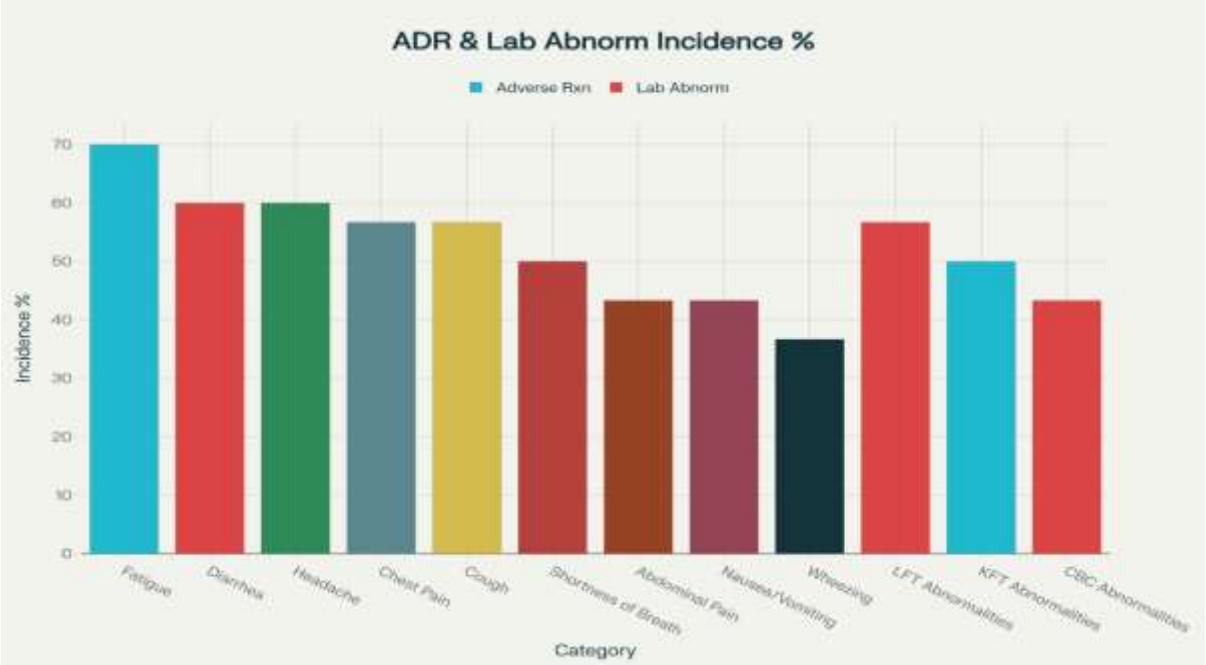

Fig:3 Frequency of Adverse Drug Reactions and Laboratory Abnormalities in Patients with Fibrotic ILD on Nintedanib Therapy

Treatment Modifications and Adherence Patterns

Treatment adherence and dosing modifications were evaluated across the study population. Of the 30 patients, 40.0% (n=12) maintained the original Nintedanib dose without modifications throughout the observation period. An equal proportion of patients (40.0%, n=12) required dose reductions due to tolerability issues, while 20.0% (n=6) experienced temporary treatment interruptions [10].

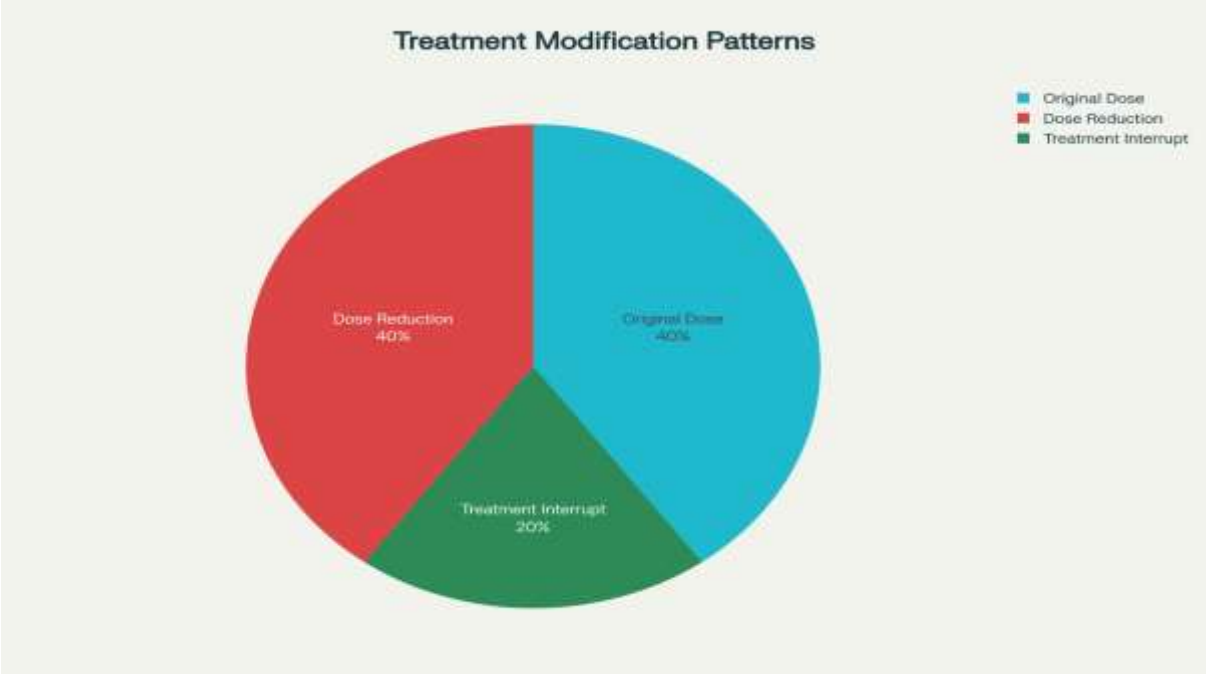

Fig: 4 Pie chart stating the dose modification needed among patients with nintedanib ADRs.

orrelation Between ADR Burden and Treatment Duration

Spearman rank correlation analysis was carried out to examine the relationship between total adverse drug reaction burden and treatment duration and observed a negative correlation between the total number of ADRs experienced by patients and their treatment duration ($\rho = -0.335$, $p = 0.071$). While this correlation did not reach conventional statistical significance ($p < 0.05$), the finding suggests a clinically meaningful trend wherein patients experiencing higher ADR frequencies may have shorter treatment durations [11,12].

Fig: 5 Scatter plot showing the negative correlation between total ADR burden and treatment duration in patients receiving Nintedanib therapy

Causality Assessment

WHO causality assessment was conducted for diarrhea in 18 affected patients. Results showed 22.2% (n=4) as "Certain," 33.3% (n=6) as "Probable," 22.2% (n=4) as "Possible," and 22.2% (n=4) as "Unlikely." The combined 55.5% of "Certain" and "Probable" cases provides strong evidence for a causal relationship between Nintedanib and gastrointestinal adverse events [13]**.**

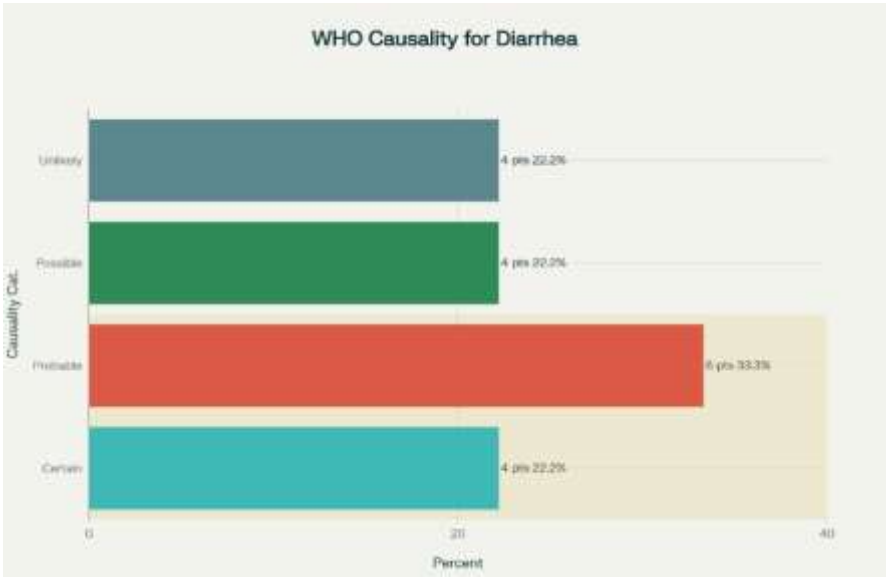

Fig 6: WHO Causality Assessment for Diarrhea in Nintedanib-Treated Patients

Clinical Management Strategies

Clinical management of Nintedanib-related adverse reactions focused on symptom-directed supportive care (e.g., pantoprazole for GI symptoms, oral rehydration for diarrhea, dietary adjustments), dynamic dose adjustments (tapering or brief interruptions for severe symptoms), and physician-led patient education to improve adherence and prompt event reporting. This individualized strategy—combining supportive pharmacotherapy, flexible dosing, and targeted counselling—enabled most patients to continue antifibrotic therapy safely [14].

DISCUSSION

Summary of Key Findings

This prospective observational study evaluated adverse drug reactions (ADRs) associated with Nintedanib therapy in 30 fibrotic interstitial lung disease patients. A high prevalence of ADRs was observed, with total 143 total events documented (mean 4.77 per patient). Fatigue (70.0%) and diarrhoea (60.0%) emerged as the most frequent adverse events, consistent with Nintedanib's established safety profile. Significant demographic associations were identified, with female sex ($p = 0.006$) and advanced age (mean 68.5 vs. 60.5 years, $p = 0.017$) representing significant risk factors for diarrhoea development. Multivariate analysis confirmed diarrhoea as the strongest predictor of dose modification ($\beta = 2.500$, $p < 0.001$), with 60% of patients requiring treatment adjustments [15].

Interpretation and Clinical Implications

The predominance of gastrointestinal and systemic ADRs reflects Nintedanib's inhibition of PDGFR, FGFR, and VEGFR, which disrupts mucosal integrity, hepatic metabolism, and vascular function. Older patients face greater GI toxicity due to reduced mucosal resilience and altered drug metabolism, while higher diarrhea rates in women may stem from sex-specific pharmacokinetics or hormonal effects. WHO causality assessment classified 55.5% of diarrhea cases as "Certain" or "Probable," underscoring the predictable, dose-dependent nature of these ADRs and supporting formal causality evaluation in antifibrotic pharmacovigilance [16,17]. In this study, 60% diarrhoea rate mirrors INPULSIS, SENSCIS, and INBUILD trials (60–75%), confirming external validity. Unlike these controlled trials, our real-world cohort included comorbid and socioeconomically diverse patients, enriching Nintedanib tolerability data in routine practice. [21, 22]High fatigue prevalence (70%) aligns with post-marketing reports of constitutional ADRs. Demographic risks in our study echo global pharmacovigilance findings in elderly, comorbid populations. By providing region-specific safety data from India, this study fills non-Western evidence gaps and supports the generalizability of Nintedanib's ADR profile [18,19].

Clinical Management and Treatment Optimization

Diarrhea's strong link to dose adjustments ($\beta=2.5$, $p<0.001$) highlights the need for early antidiarrheal therapy, hydration, and dietary changes to reduce GI toxicity and extend treatment. Although the negative correlation between ADR burden and duration ($\rho=-0.335$, $p=0.071$) wasn't statistically significant, it suggests that cumulative side effects can shorten therapy, underscoring the value of vigilant ADR monitoring and personalized management. With 60% of patients requiring dose modifications (40% reductions, 20% interruptions), our findings affirm that Nintedanib ADRs are controllable through timely clinical interventions [20] [23]

CONCLUSION

WHO causality assessment classified the majority of diarrhea episodes as "Certain" or "Probable," reinforcing Nintedanib's causal role in these events. These findings corroborate global safety data while providing novel region-specific evidence in an Indian cohort characterized by diverse comorbidities and socioeconomic backgrounds. The results underscore the importance of proactive ADR mitigation—through early intervention, individualized monitoring, and structured patient counselling—to maintain treatment adherence and optimize clinical outcomes.

This study underscores the necessity of systematic ADR monitoring, early identification of high-risk patients (e.g., elderly, female), and proactive management in Nintedanib therapy. A multidisciplinary approach—engaging clinical pharmacists, structured patient education, and regular follow-up—can mitigate the substantial but manageable ADR burden. Health systems should establish standardized ADR assessment and intervention protocols to safeguard safety and optimize outcomes. In resource-limited settings, targeted education and streamlined monitoring offer cost-effective means to enhance adherence and reduce ADR-related therapy discontinuations

Future research should involve larger, multicentre cohorts to validate predictive risk models and evaluate standardized ADR management protocols. Integration of pharmacogenomic and biomarker-driven approaches may further personalize Nintedanib therapy and enhance long-term tolerability in fibrotic ILD populations [30].

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