



doi • 10.5578/tt.2026031271
Tuberk Toraks 2026;74(3):127-137
Received: 22.05.2026 • Accepted: 21.08.2026

RESEARCH ARTICLE

Real-world effectiveness and safety of nintedanib in connective tissue disease–associated interstitial lung disease: Retrospective cohort study

Ayşenur YILMAZ^{1,2}(ID)
Erdem BEKTAŞ^{1,2}(ID)
Barış DEMİRKOL³(ID)
Ramazan EREN⁴(ID)
Umut İLHAN⁴(ID)
Erdoğan ÇETİNKAYA⁴(ID)
Cemal BEŞ¹(ID)

¹ Department of Rheumatology, Basakşehir Cam and Sakura City Hospital, University of Health Sciences, İstanbul, Türkiye
² Department of Immunology, Istanbul University Aziz Sancar Institute of Experimental Medicine, İstanbul, Türkiye
³ Department of Chest Diseases, Basakşehir Cam and Sakura City Hospital, University of Health Sciences, İstanbul, Türkiye
⁴ Department of Chest Diseases, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, University of Health Sciences, İstanbul, Türkiye

Cite this article as: Yılmaz A, Bektaş E, Demirkol B, Eren R, İlhan U, Çetinkaya E, et al. Real-world effectiveness and safety of nintedanib in connective tissue disease–associated interstitial lung disease: Retrospective cohort study. *Tuberk Toraks* 2026;74(3):127-137.

Address for Correspondence

Dr. Ayşenur YILMAZ
Department of Rheumatology,
Basakşehir Çam and Sakura City Hospital,
University of Health Sciences
İSTANBUL-TÜRKİYE
e-mail: yilmazanur@gmail.com

This is an open-access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes (<http://creativecommons.org/licenses/by-nc/4.0/>).

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

©Copyright 2026 by Tuberculosis and Thorax.
Available online at www.tuberktoraks.org

ABSTRACT

Real-world effectiveness and safety of nintedanib in connective tissue disease–associated interstitial lung disease: Retrospective cohort study

Introduction: Nintedanib, a multi-tyrosine kinase inhibitor, has demonstrated efficacy in reducing lung function decline in progressive fibrosing interstitial lung disease (ILD). However, real-world evidence in heterogeneous connective tissue disease (CTD) –associated ILD populations, particularly under immunosuppressive (IS) therapy, remains limited. This study aimed to evaluate the effectiveness, safety, and treatment retention of nintedanib across CTD-ILD.

Materials and Methods: Single-center retrospective cohort included 42 patients with CTD-ILD who initiated nintedanib between January 2020-January 2025. Baseline characteristics, pulmonary function tests, radiological findings, adverse events (AEs), and treatment retention were analyzed. Patients were stratified as stable [absence of ≥5% forced vital capacity (FVC) decline] or progressive based on 12-month follow-up. Inter-group comparisons were performed. Drug survival was assessed using Kaplan–Meier estimates.

Results: The cohort comprised idiopathic pneumonia with autoimmune features (41%), systemic sclerosis (29%), rheumatoid arthritis (19%), and Sjögren's disease (7%). Nintedanib was initiated after IS in 82% of the cases. Median treatment duration was 17 months. At 12 months, FVC% remained stable [62 (55–73) to 66 (54–76), $p=0.929$] and diffusing capacity of the lung for carbon monoxide (DLCO%) showed no significant change [37 (27–54) to 40 (24–45), $p=0.448$]. Diarrhea was the most frequent AE (33%), and discontinuation occurred in 6 patients (14%). 12-month retention exceeded 85%. No significant differences were observed between stable ($n=24$) and progressive ($n=11$) groups.

Conclusion: In this real-world cohort, predominantly pretreated with IS, nintedanib was associated with functional stabilization and good tolerability across diverse subtypes. Low rates of diarrhea and high treatment retention support the feasibility of antifibrotic IS integration in progressive CTD-ILD care.

Key words: Nintedanib; connective tissue disease; interstitial lung disease; real-life data; antifibrotic therapy; immunosuppressive therapy

ÖZ

Romatolojik hastalıklara bağlı interstisyel akciğer hastalıklarında nintedanib: Gerçek yaşam deneyimi

Giriş: Nintedanib, progresif fibrotik interstisyel akciğer hastalığında (İAH) akciğer fonksiyon kaybını azaltmada etkinliği gösterilmiş bir antifibrotik ajandır. Ancak özellikle immünsupresif (İS) tedavi altındaki heterojen bağ dokusu hastalığına bağlı interstisyel akciğer hastalığı (CTD-İAH) popülasyonlarında gerçek yaşam verileri sınırlıdır. Bu çalışmada, CTD-İAH hastalarında nintedanibin etkinliği, güvenliliği ve tedavi sürdürülme oranı değerlendirildi.

Materyal ve Metod: Bu tek merkezli retrospektif kohort çalışmasına, Ocak 2020–Ocak 2025 tarihleri arasında nintedanib başlanan 42 CTD-İAH hastası dahil edildi. Demografik özellikler, solunum fonksiyon testleri, radyolojik bulgular, advers olaylar ve tedavi sürdürülme oranı analiz edildi. Hastalar, 12 aylık izlemede $\geq 5\%$ zorlu vital kapasite (FVC) düşüşü olmamasına göre stabil, varlığına göre progresif olarak sınıflandırıldı. Gruplar arası karşılaştırmalar yapıldı ve ilaç sağkalımı Kaplan–Meier yöntemi ile değerlendirildi.

Bulgular: Kohortta en sık alt gruplar idiyopatik otoimmün özellikli pnömoni (%41), sistemik skleroz (%29), romatoid artrit (%19) ve sjögren hastalığı (%7) idi. Olguların %82'sinde nintedanib, İS tedavi sonrasında başlandı. Medyan tedavi süresi 17 ay idi. On ikinci ayda %FVC stabil kaldı [62 (55–73)'den 66 (54–76)'ya; $p=0,929$] ve karbonmonoksit akciğer difüzyon kapasitesi (DLCO%)'da anlamlı değişiklik izlenmedi [37 (27–54)'den 40 (24–45)'a; $p=0,448$]. En sık advers olay diyare (%33) olup, %14 hastada tedavi kesildi. On iki aylık tedavi sürdürülme oranı %85'in üzerindeydi. Stabil ($n=24$) ve progresif ($n=11$) gruplar arasında anlamlı fark saptanmadı.

Sonuç: Gerçek yaşam verilerini yansıtan ve çoğunluğu İS tedavi almış bu kohortta, nintedanib farklı CTD-İAH alt tiplerinde fonksiyonel stabilizasyon ve iyi tolere edilebilirlik ile ilişkili bulunmuştur. Düşük diyare oranları ve yüksek tedavi sürdürülme oranı, progresif CTD-İAH yönetiminde antifibrotik ve immünsupresif tedavilerin birlikte kullanımının uygulanabilirliğini desteklemektedir.

Anahtar kelimeler: Nintedanib; bağ dokusu hastalığı; interstisyel akciğer hastalığı; gerçek yaşam verisi; antifibrotik tedavi; immünsupresif tedavi

INTRODUCTION

Connective tissue disease (CTD)–associated interstitial lung disease (ILD) is a leading cause of morbidity and mortality among patients with systemic autoimmune diseases. Lung involvement occurs in systemic sclerosis (SSc), rheumatoid arthritis (RA), idiopathic pneumonia with autoimmune features (IPAF), Sjögren's disease (SjD), idiopathic inflammatory myopathies (IIM), and mixed connective tissue disease (MCTD). According to recent European Respiratory Society (ERS)/European Alliance of Associations for Rheumatology (EULAR) and American College of Rheumatology (ACR)/American College of Chest Physicians (CHEST) guidelines, RA-ILD is recognized within the CTD-ILD spectrum due to overlapping autoimmune mechanisms and fibrosing trajectories (1,2). Despite heterogeneity across disease subtypes, progressive fibrosing phenotypes are common and associated with impaired quality of life and reduced survival (3).

The dual inflammatory–fibrotic nature of CTD-ILD complicates management. Immunosuppressants such as mycophenolate mofetil (MMF), azathioprine, cyclophosphamide, calcineurin inhibitors, JAK inhibi-

tors and biologics (rituximab, tocilizumab, etc.) target inflammation, yet some patients develop fibrotic progression despite therapy (4). Antifibrotic agents originally developed for idiopathic pulmonary fibrosis (IPF) have thus gained importance. Nintedanib, a tyrosine kinase inhibitor of vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor (FGFR), and platelet-derived growth factor receptor (PDGFR), suppresses fibroblast proliferation and extracellular matrix deposition (5).

Randomized controlled trials have established the efficacy of nintedanib in reducing forced vital capacity (FVC) decline in both progressive fibrosing (PF)-ILD and SSc-ILD. In the INBUILD study, nintedanib slowed annual FVC decline by approximately 100 mL compared to placebo in autoimmune PF-ILD subgroups (3). The SENSICIS trial and its 3-year extension confirmed long-term safety and sustained efficacy in SSc-ILD (4).

Beyond clinical trials, multiple real-world studies have confirmed the effectiveness and safety of nintedanib across heterogeneous CTD-ILD populations. In a single-center Turkish cohort, lung function remained stable and adverse events (AEs) were manageable (6). A

multicenter study in Spain demonstrated comparable stability in RA-ILD patients with high 12-month drug retention (7). Additional observational cohorts from Europe and Asia support these findings across RA-ILD and SSc-ILD subsets, often in combination with immunosuppressive (IS) agents such as MMF or rituximab (8-10).

However, real-world data remain scarce for mixed CTD-ILD cohorts receiving concomitant immunosuppression. This single-center cohort from Türkiye aimed to evaluate the real-life effectiveness, safety, and treatment retention of nintedanib in a heterogeneous CTD-ILD population, and to identify clinical characteristics associated with stable versus progressive disease courses.

MATERIALS and METHODS

Study Design and Setting

This was a single-center, retrospective observational study conducted at a tertiary rheumatology clinic in Türkiye. Patients with CTD-ILD who initiated nintedanib therapy between January 2020 and January 2025 were included in the study. The study protocol was approved by the local ethics committee (2025-45, 05.02.2025) and was carried out in accordance with the Declaration of Helsinki.

Patient Population

A total of 42 patients were included in the study. Patients were identified from a broader cohort of individuals who had been prescribed nintedanib in routine clinical practice for the indication of progressive pulmonary fibrosis (PPF). PPF was defined in accordance with American Thoracic Society (ATS)/European Respiratory Society (ERS) guidance as evidence of progression within the previous 12 months, demonstrated by (1) an absolute decline in FVC of $\geq 5\%$, (2) worsening respiratory symptoms, or (3) radiological progression of fibrotic changes on high-resolution computed tomography (HRCT) (11). Eligible patients were adults (≥ 18 years old) with a confirmed diagnosis of a rheumatic disease (SSc, RA, IPAF, SjD, inflammatory myositis etc.) and ILD verified by HRCT, who had baseline pulmonary function tests (PFTs) data and at least six months of follow-up after nintedanib initiation. Rheumatic diseases were classified according to the established criteria: the 2013 ACR/EULAR criteria for SSc, 2010 ACR/EULAR criteria for RA, 2016 ACR/EULAR criteria for SjD, 2017 EULAR/ACR criteria for inflammatory myopathies, and 2015 ERS/

ATS research criteria for IPAF. From the initial cohort, patients with alternative predominant lung diseases [such as advanced Chronic Obstructive Pulmonary Disease (COPD), active infection, or malignancy], incomplete clinical records, or follow-up shorter than six months were excluded from the study. The study included all consecutive eligible patients who initiated nintedanib during the study period.

Data Collection

Data were extracted retrospectively from electronic medical records and patient charts. The collected variables included demographic and clinical characteristics, such as age, sex, smoking status, disease duration, and the timing of ILD in relation to the onset of the underlying rheumatic disease. The underlying rheumatologic diagnoses were SSc, RA, IPAF, SjD, and other connective tissue diseases. Radiological patterns on HRCT were categorized as usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), lymphoid interstitial pneumonia (LIP), or other, based on joint assessment by a rheumatologist experienced in interstitial lung disease and a radiologist routinely involved in thoracic imaging interpretation according to ATS/ERS HRCT pattern definitions (11). Potential sources of bias, including selection bias and information bias inherent to the retrospective design, were acknowledged and minimized through standardized data collection and pre-defined inclusion criteria.

Treatment-related information included the prior and concomitant use of IS agents, as well as glucocorticoids. Details of nintedanib therapy were recorded, including starting dose (150 or 100 mg twice daily), total treatment duration, dose modifications, temporary interruptions, and reasons for discontinuation. Any AEs observed during follow-up were also documented.

Functional and radiological assessments were systematically reviewed. PFTs FVC, forced expiratory volume in one second (FEV_1), and diffusing capacity of the lung for carbon monoxide (DLCO-%). FVC and FEV_1 were expressed in liters and as a percentage of the predicted value. Radiological features on HRCT were evaluated at baseline and during follow-up for the presence of ground-glass opacities, honeycombing, reticular abnormalities, traction bronchiectasis, and septal thickening. Additional parameters included the six-minute walk test (6MWT), supplemental oxygen use, malignancy development, and mortality.

Pulmonary hypertension (PAH) was assessed based on echocardiographic evaluation.

Progressive ILD was defined as an absolute decline of $\geq 5\%$ in predicted FVC during follow-up. Patients who did not meet this threshold were classified as having stable ILD. Due to the limited sample size and heterogeneous follow-up durations, $\geq 5\%$ FVC decline was selected as the primary criterion for progression, and the use of a broader composite endpoint incorporating clinical or radiologic worsening was not feasible (11). Consequently, only patients with at least 12 months of follow-up were eligible for classification as progressive or stable, whereas individuals with shorter follow-up contributed only baseline data to the analysis. Stable versus progressive subgroup analyses were restricted to 35 patients with at least 12 months of follow-up; seven patients with shorter follow-up were excluded from these analyses. Drug retention was defined as the time from nintedanib initiation to permanent discontinuation for any cause, and patients were censored at their last available follow-up visit. Patients who had missing pulmonary function data or who did not meet the minimum follow-up requirement were excluded from the relevant outcome analyses.

Statistical Analysis

Continuous variables were summarized as mean $\pm$ standard deviation (SD) or median (interquartile range, IQR). Categorical variables were summarized as frequencies and percentages. Normality of distribution was tested using the Shapiro–Wilk test. Subgroup analyses were performed comparing patients with stable and progressive disease. Depending on the distribution, inter-group comparisons were performed using the independent samples t-test or the Mann–Whitney U test for continuous variables and the Chi-square or Fisher–Freeman–Halton test for categorical variables. Changes within groups over time were analyzed using the Wilcoxon signed-rank test and the McNemar test. Drug retention was assessed using Kaplan–Meier survival analysis, and differences between the groups were compared using the log-rank test. Patients lost to follow-up were censored at their last available visit, and those with insufficient follow-up were excluded from subgroup analyses. All analyses were performed using International Business Machines (IBM) Statistical Package for the Social (SPSS) Statistics (version 30) and GraphPad Prism (version 10). A two-sided p-value of less than 0.05 was considered statistically significant.

Guidance

This study was conducted and reported in accordance with the strengthening the reporting of observational studies in epidemiology (STROBE) guidelines.

RESULTS

Demographic and Baseline Characteristics

A total of 42 patients with CTD-ILD treated with nintedanib were included. Median age was 69 years (IQR 56–76). Twenty-six patients (62%) were female, and 16 (38%) were male. Regarding smoking status, 28 (67%) were never smokers, 11 (26%) ex-smokers, and 3 (7%) current smokers.

The underlying rheumatic diagnoses were IPAF in 17 (41%), SSC in 12 (29%), RA in 8 (19%), SjD in 3 (7%), and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis in 2 (5%). Median age at ILD diagnosis was 64 years (53–70). Median age at rheumatic disease diagnosis was 62 years (48–70). ILD preceded the diagnosis of the rheumatic disease in 23 patients (55%). Both diagnoses were simultaneous in 10 patients (24%), while the rheumatic disease was diagnosed before ILD in 9 patients (21%). PAH was documented in 11 patients (26%).

Radiological Findings

HRCT patterns included UIP in 23 (55%) and NSIP in 17 (41%). One patient (2%) had lymphocytic interstitial pneumonia (LIP), and one (2%) had an unclassifiable pattern. Reticular abnormalities were universal (42/42, 100%), septal thickening was observed in 41 (98%), traction bronchiectasis in 38 (91%), ground-glass opacities in 37 (88%), and honeycombing in 26 (62%).

Subgroup Comparisons: Stable vs Progressive ILD

Patients were stratified into stable ILD ($n = 24$) and progressive ILD ($n = 11$). There were no statistically significant differences between the groups in terms of sex distribution, smoking status, median age, timing of ILD and rheumatic disease onset, rheumatic disease subtype, presence of PAH, or HRCT pattern distribution (all $p > 0.05$) (Table 1).

Concomitant Therapies

Glucocorticoids were used in 39 patients (93%). IS was administered in 33 (79%); MMF in 27 (64%), rituximab in 7 (17%), azathioprine in 6 (14%), cyclophosphamide in 4 (10%), and tocilizumab in 3 (7%). Nine patients (21%) received more than one

Table 1. Baseline characteristics

	All patients	Stable	Progressive	p
	n= 42	n= 24	n= 11	
Female, n (%)	26 (62)	17 (71)	7 (64)	0.709*
Smoking status, n (%)				0.470 ^Ŷ
Smoker	3 (7)	0	1 (9)	
Ex-smoker	11 (26)	6 (25)	2 (18)	
Never-smoker	28 (67)	18 (75)	8 (73)	
Age, med (IQR)	69 (56-76)	65 (57-75)	56 (47-76)	0.302 ^Ŷ
ILD-Rheumatic disease, n (%)				0.275 ^Ŷ
ILD preceding	23 (55)	12 (50)	9 (82)	
Simultaneous onset	10 (24)	6 (25)	1 (9)	
Rheumatic disease preceding	9 (21)	6 (25)	1 (9)	
Rheumatic disease, n (%)				0.675 ^Ŷ
IPAF	17 (41)	8 (33)	5 (46)	
SSc	12 (29)	10 (42)	2 (18)	
RA	8 (19)	3 (13)	2 (18)	
Sjogren's disease	3 (7)	2 (8)	1 (9)	
AAV	2 (5)	1 (4)	1 (9)	
ILD pattern (HRCT), n (%)				0.722 ^Ŷ
UIP	23 (55)	12 (50)	6 (55)	
NSIP	17 (41)	11 (46)	4 (37)	
LIP	1 (2)	1 (4)	0	
Other	1 (2)	0	1 (9)	
HRCT findings, n (%)				
Ground-glass opacity	37 (88)	20 (83)	10 (91)	1.000*
Honeycombing	26 (62)	14 (58)	7 (64)	1.000*
Reticular pattern	42 (100)	24 (100)	11 (100)	N/A
Traction bronchiectasis	38 (91)	20 (83)	11 (100)	0.285*
Septal thickening	41 (98)	24 (100)	10 (91)	0.314*

*: Fisher's exact test, ^Ŷ: Fisher Freeman Halton test, ^Ŷ: Mann-Whitney U.

AAV: ANCA associated vasculitis, HRCT: High resolution computed tomography, ILD: Interstitial lung disease, IPAF: Interstitial pneumonia with auto-immune features, IQR: Interquartile range, LIP: Lymphocytic interstitial pneumonia, Med: Median, n: Number of patients, NSIP: Nonspecific interstitial pneumonia, RA: Rheumatoid arthritis, UIP: Usual interstitial pneumonia. Subgroup analyses included 35 patients with ≥12 months of follow-up.

IS agent. IS was started after nintedanib in 5 patients (15%), concurrently in 1 (3%), and before nintedanib initiation in 27 (82%). Median duration of nintedanib treatment was 17 months (IQR 12–28). There were no significant differences between stable and progressive groups regarding concomitant treatment patterns (Table 2).

Safety and Clinical Outcomes

AEs were recorded in 18 patients (43%). Diarrhea was reported in 14 (78% of those with AEs elevat-

ed transaminases in 2 (11%), and other events in 2 (11%). Dose reduction was needed in 7 patients (17%), and discontinuation due to AEs occurred in 6 (14%). During follow-up, 7 patients (17%) developed a new requirement for supplemental oxygen, 3 (7%) were diagnosed with malignancy, and 9 (21%) died. There were no significant differences between stable and progressive ILD groups in terms of concomitant treatments, timing of IS use, AEs, or clinical outcomes (all p> 0.05). Details are shown in Table 2.

Table 2. Treatment details and outcomes

	All patients	Stable	Progressive	p
	n= 42	n= 24	n= 11	
Glucocorticoid use, n (%)	39 (93)	21 (88)	11 (100)	0.536*
Immunosuppressive use, n (%)	33 (79)	21 (88)	9 (82)	0.640*
MMF, n (%)	27 (64)	18 (75)	8 (73)	1.000*
Azathioprine, n (%)	6 (14)	5 (21)	0	0.157*
Rituximab, n (%)	7 (17)	5 (21)	1 (9)	0.640*
Cyclophosphamide, n (%)	4 (10)	4 (17)	0	0.285*
Tocilizumab, n (%)	3 (7)	1 (4)	1 (9)	0.536*
Timing of nintedanib				0.219 ^Y
Before IS, n/N (%)	5/33 (15)	4/21 (19)	0	
Concurrent use, n/N (%)	1/33 (3)	0	1/9 (11)	
After IS, n/N (%)	27/33 (82)	17/21 (81)	8/9 (89)	
Nintedanib duration, med (IQR), m	17 (12–28)	24 (17–36)	15 (13–21)	0.091 ^Y
Adverse events, n (%)	18 (43)	12 (50)	4 (36)	0.493*
Diarrhea, n/N (%)	14/18 (78)	9/12 (75)	3/4 (75)	0.486 ^Y
Elevated transaminases, n/N (%)	2/18 (11)	2/12 (17)	0	0.486 ^Y
Other, n/N (%)	2/18 (11)	1/12 (8)	1 (25)	0.486 ^Y
Low-dose nintedanib, n (%)	7 (17)	4 (17)	1 (9)	1.000*
Adverse event leading to drug discontinuation, n (%)	6 (14)	3 (13)	2 (18)	1.000*
Oxygen requirement, n (%)	7 (17)	4 (17)	3 (27)	0.652*
Malignancy, n (%)	3 (7)	2 (8)	1 (9)	1.000*
Death, n (%)	9 (21)	4 (17)	1 (9)	1.000*

*: Fisher's exact test, ^Y: Fisher Freeman Halton test, ^Y: Mann-Whitney U.

IQR: Interquartile range, IS: Immunosuppressive treatment, Med: Median, m: Months, MMF: Mycophenolate mofetil, n: Number of patients, N: Number of available patients. Subgroup analyses included 35 patients with ≥12 months of follow-up.

Pulmonary Function, Exercise Capacity, and Radiological Changes

Pulmonary function tests remained overall stable during treatment. At baseline, median FVC% was 62 (55–73). At 12 months, FVC% was 66 (54–76) ($p=0.929$). FVC volume at baseline was 1.69 L (1.38–2.34). At 12 months, FVC volume was 1.76 L (1.38–2.10) ($p=0.242$). Baseline FEV₁% was 67 (55–75). At 12 months, FEV₁% was 68 (53–80) ($p=0.381$). Baseline FEV₁ volume was 1.46 L (1.29–1.97). At 12 months, FEV₁ volume was 1.48 L (1.18–1.81) ($p=0.086$). DLCO-% values were available in 17 patients. At baseline, DLCO-% was 37% (27–54). At 12 months, DLCO-% was 40% (24–45) ($p=0.448$). These pulmonary function results are shown in Figure 1A–E. Supplemental Digital Content 1 provides additional pre-treatment measurements available in a subset of patients.

Exercise capacity was assessed by 6-minute walking test. In 12 patients with available data, median 6-minute walking distance was 360 m (334–415) at baseline and 388 m (288–435) at 12 months ($p=0.638$). In 18 patients with available desaturation data, no significant differences were observed between baseline and 12 months.

During follow-up, new HRCT abnormalities developed in a limited number of patients. Ground-glass opacities were observed in 3 patients. Traction bronchiectasis was observed in 3 patients. Honeycombing was observed in 1 patient. Septal thickening was observed in 1 patient. Reticular abnormalities were present in all patients at baseline and persisted during follow-up.

Hematological parameters, including white blood cell count, neutrophil count, lymphocyte count, hemoglobin, and platelet count, showed no significant

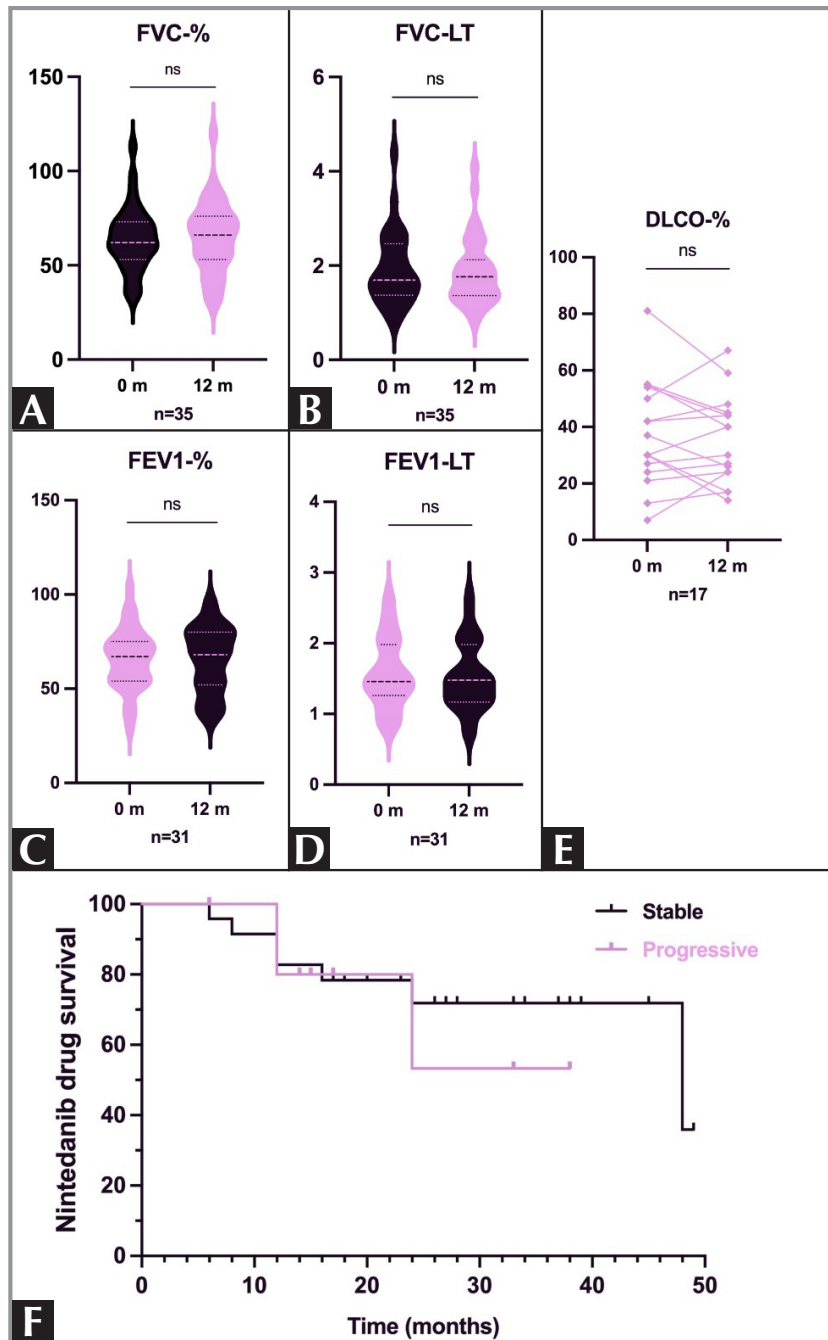


Figure 1. Longitudinal changes in pulmonary function and treatment retention in patients with CTD-ILD receiving nintedanib Violin plots illustrate the distribution and median values of pulmonary function parameters at baseline (0 months) and 12 months following nintedanib initiation. (A) Forced vital capacity (FVC, % predicted), (B) FVC (L), (C) forced expiratory volume in one second (FEV₁, % predicted), and (D) FEV₁ (L) remained stable over the 12-month follow-up period, with no statistically significant differences (ns). (E) In a subset of patients with available data (n= 17), the diffusing capacity for carbon monoxide (DLCO, % predicted) also demonstrated no significant change at 12 months. (F) Kaplan-Meier analysis of drug survival revealed high treatment retention rates, with no significant difference between patients classified as stable and those with progressive interstitial lung disease (ILD). Overall, these findings indicate sustained pulmonary function and excellent treatment persistence under real-world conditions. ns: non-significant.

changes between baseline and 12 months. Renal function assessed by glomerular filtration rate also remained stable. Liver enzymes [aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP)] and lactate dehydrogenase (LDH) values did not show significant variation during follow-up. In contrast, a significant increase was observed in gamma-glutamyl transferase (GGT) ($p=0.033$) and c-reactive protein (CRP) ($p=0.030$). Detailed laboratory values are provided in Supplementary Table S1.

Kaplan–Meier analysis demonstrated high drug survival on nintedanib. There was no significant difference between patients with stable and progressive ILD (Figure 1F).

DISCUSSION

In this real-world CTD-ILD cohort with a predominantly immunosuppression-pretreated profile (82%), nintedanib was well tolerated and showed a reassuring safety pattern. Despite the heterogeneous disease spectrum and high IS burden, FVC values remained generally stable over follow-up without a clinically relevant decline, reflecting preservation rather than deterioration of lung function. This is notable given that antifibrotic therapy was initiated in patients fulfilling a PPF profile, a scenario frequently encountered in daily practice where inflammation is first addressed with IS and antifibrotics are subsequently added. Within this pragmatic context, current recommendations permit nintedanib use (alone or in combination with background IS) when progression is observed (1,2,12,13).

In our cohort, FVC and DLCO-% remained largely stable during follow-up, a pattern that is compatible with the expected trajectory under antifibrotic therapy. In INBUILD, nintedanib reduced the annual FVC decline in autoimmune PF-ILD (80.8 vs 187.8 mL/year), and in SENSICIS, a 44% relative reduction was demonstrated in SSc-ILD (52.4 vs 93.3 mL/year) (4,14). Long-term SENSICIS-ON data further confirmed sustained safety and a consistent treatment effect (15). These pivotal studies, together with the observations by Khanna et al. showing broad benefit and feasibility alongside IS therapy, provide contextual evidence for antifibrotic use in autoimmune ILD (16). Although our real-world CTD-ILD cohort is smaller and more heterogeneous (including RA-ILD, SSc-ILD, IPAF, and SjD-ILD) the absence of a meaningful decline in pulmonary function aligns with these data and suggests

that nintedanib may help maintain stability across diverse CTD-ILD subtypes encountered in daily practice. Similarly, advanced-stage IPF data suggest that survival is driven more by disease severity than by antifibrotic choice, reinforcing that nintedanib's primary benefit lies in functional stabilization rather than mortality modification (17).

Consistency with regional real-world experience also reinforces the strength of our observations. Misirci et al. reported preserved FVC and DLCO-% with diarrhea rates around 30%, and a Japanese cohort demonstrated more favorable outcomes when nintedanib was combined with background immunosuppression (18,19). A Middle Eastern systemic autoimmune rheumatic disease (SARD)-ILD study of 47 patients showed sustained functional stability over 24 months, whereas our cohort provides complementary evidence in a uniquely IS-pretreated and heterogeneous CTD-ILD population (20). Likewise, Spanish and Indian real-world data reported high 12-month retention and stabilization with nintedanib, including when used alongside MMF or cyclophosphamide (CYC) (7,9). Together with reports from Japan and Greece, these results highlight the consistent real-world applicability of antifibrotic therapy across diverse CTD-ILD settings (21,22). Importantly, despite the highest rate of prior IS exposure reported to date, our cohort achieved stabilization comparable to these international datasets, supporting the notion that nintedanib remains effective and well tolerated even after prolonged immune modulation.

Diarrhea, the most common AE, occurred in 33% of our patients, substantially lower than reported in pivotal randomized controlled trials and Asian cohorts (typically 67–76%) (4,14,23). This aligns with real-world data from other regions, where discontinuation rates have generally remained below 10%, underscoring the favorable tolerability profile of nintedanib in routine practice (6,22). This safety pattern is also consistent with a recent meta-analysis demonstrating that, although nintedanib and pirfenidone offer comparable overall effectiveness, nintedanib displays a distinct but predictable AE profile, dominated by gastrointestinal and hepatic events, without compromising treatment continuity (24). As observed in previous studies, proactive management and timely dose adjustments were key factors in maintaining adherence and tolerability in our cohort (25–27). Recent network meta-analyses further support this safety signal, indicating that nintedanib (whether used alone or with MMF) was associated with improvements in

FVC% predicted without increasing the risk of treatment discontinuation (28).

Mechanistically, nintedanib targets key pro-fibrotic pathways (VEGFR, FGFR, PDGFR) and modulates NLR family pyrin domain containing 3 (NLRP3) inflammasome activity, providing a biologically plausible rationale for its use in fibrosing ILD (2,5). In our cohort, several patients who had shown limited response to prior immunosuppression achieved stabilization following antifibrotic escalation, suggesting that nintedanib may offer additional benefit in CTD-ILD with a PPF phenotype (8,29). When interpreted alongside previous real-world cohorts, these findings support the effectiveness, safety, and feasibility of nintedanib alone or combined with background IS across a broader CTD-ILD spectrum, extending its practical applicability beyond SSc-ILD (16,19,22).

This study offers several strengths that enhance its real-world relevance. The cohort was notably heterogeneous, encompassing CTD-ILD subtypes often underrepresented in clinical trials, and the exceptionally high rate of prior IS exposure (82%) mirrors the therapeutic sequences encountered in routine care. Additionally, the consistently favorable tolerability profile (particularly the low diarrhea rate and high treatment retention) supports the practical feasibility of nintedanib in everyday clinical settings.

At the same time, important limitations must be acknowledged. The single-center, retrospective design and modest sample size constrained the depth of subgroup comparisons, and lung function trajectories were assessed without repeated longitudinal measurements. Moreover, the absence of comparison groups (such as patients managed with immunosuppression alone or those not receiving antifibrotic therapy) limits the ability to draw causal inferences. Future prospective, multicenter studies with structured follow-up and predefined control arms will be needed to address these gaps.

Despite these limitations, the study contributes meaningful real-world evidence, suggesting that nintedanib can be safely and feasibly incorporated into the management of diverse CTD-ILD profiles encountered in daily rheumatology practice.

Ethical Committee Approval: The study protocol was approved by the Başakşehir Çam and Sakura City Hospital Clinical Research Ethics Committee (Decision no: 45, Date: 05.02.2025)

Peer-review: Externally peer-reviewed.

CONFLICT of INTEREST

The authors declare that they have no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: AY, EB, CB

Analysis/Interpretation: AY, EB, BD, RE, Uİ

Data Acquisition: AY, EB, BD, RE, Uİ

Writing: AY, CB

Clinical Revision: AY, EB, EÇ, CB

Final Approval: All of authors

REFERENCES

1. Johnson SR, Bernstein EJ, Bolster MB, Chung JH, Danoff SK, George MD, et al. 2023 American College of Rheumatology (ACR)/American College of Chest Physicians (CHEST) Guideline for the Treatment of Interstitial Lung Disease in People with Systemic Autoimmune Rheumatic Diseases. *Arthritis Care Res (Hoboken)* 2024; 76(8): 1051-69. <https://doi.org/10.1002/acr.25348>
2. Antoniou KM, Distler O, Gheorghiu AM, Moor CC, Vikse J, Bizymi N, et al. ERS/EULAR clinical practice guidelines for connective tissue disease-associated interstitial lung disease. Developed by the task force for connective tissue disease-associated interstitial lung disease of the European Respiratory Society (ERS) and the European Alliance of Associations for Rheumatology (EULAR). Endorsed by the European Reference Network on rare respiratory diseases (ERN-LUNG). *Eur Respir J* 2025. <https://doi.org/10.1183/13993003.02533-2024>
3. Matteson EL, Kelly C, Distler JHW, Hoffmann-Vold AM, Seibold JR, Mittoo S, et al. Nintedanib in Patients With Autoimmune Disease-Related Progressive Fibrosing Interstitial Lung Diseases: Subgroup Analysis of the INBUILD Trial. *Arthritis Rheumatol* 2022; 74(6): 1039-47. <https://doi.org/10.1002/art.42075>
4. Distler O, Highland KB, Gahlemann M, Azuma A, Fischer A, Mayes MD, et al. Nintedanib for Systemic Sclerosis-Associated Interstitial Lung Disease. *N Engl J Med* 2019; 380(26): 2518-28. <https://doi.org/10.1056/NEJMoa1903076>
5. Wu YT, Li QZ, Wu YQ, Mu M, Wu H, Tian HY, et al. Nintedanib attenuates NLRP3 inflammasome-driven liver fibrosis by targeting Src signaling. *Int Immunopharmacol* 2024; 143(Pt 3): 113630. <https://doi.org/10.1016/j.intimp.2024.113630>

6. Tekgoz E, Colak SY, Gunes EC, Ocal N, Cinar M, Yilmaz S. Nintedanib and its combination with immunosuppressives in connective tissue disease-related interstitial lung diseases. *Ir J Med Sci* 2025; 194(1): 391-7. <https://doi.org/10.1007/s11845-024-03848-6>
7. Atienza-Mateo B, Serrano-Combarro A, Loarce Martos J, Vegas-Revenge N, Martin Lopez M, Castaneda S, et al. Real-world evidence of the antifibrotic nintedanib in rheumatoid arthritis-interstitial lung disease. National multicenter study of 74 patients. *Semin Arthritis Rheum* 2025; 72: 152710. <https://doi.org/10.1016/j.semarthrit.2025.152710>
8. Zanatta E, Moccaldi B, Szucs G, Spagnolo P. Should we use nintedanib as early therapy in patients with SSC-ILD? *Autoimmun Rev* 2024; 23(1): 103463. <https://doi.org/10.1016/j.autrev.2023.103463>
9. Behera AK, Sharma P, Tg R, Kumar V, Pati SK, Sinha K. Real-World Clinical Profile and Safety of Nintedanib in Systemic Sclerosis-Associated Interstitial Lung Disease: A Subgroup Analysis of Interstitial Lung Disease Data From an Interstitial Lung Disease (ILD) Specialty Clinic in India. *Cureus* 2024; 16(7): e65579. <https://doi.org/10.7759/cureus.65579>
10. Sebastiani M, Lepri G, Iannone C, Cassione EB, Gugini G, Lo Monaco A, et al. Nintedanib in Rheumatoid Arthritis-Related Interstitial Lung Disease: Real-World Safety Profile and Risk of Side Effects and Discontinuation. *J Rheumatol* 2025; 52(5): 420-5. <https://doi.org/10.3899/jrheum.2024-0976>
11. Raghu G, Remy-Jardin M, Richeldi L, Thomson CC, Inoue Y, Johkoh T, et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. *Am J Respir Crit Care Med* 2022; 205(9): e18-e47.
12. Kondoh Y, Fujii T, Inoue Y, Atsumi T. Unmet needs and emerging pharmacotherapies for autoimmune connective tissue disease-associated interstitial lung diseases. *Autoimmun Rev* 2025; 24(11): 103900. <https://doi.org/10.1016/j.autrev.2025.103900>
13. Ahmed S, Handa R. Management of Connective Tissue Disease-related Interstitial Lung Disease. *Curr Pulmonol Rep* 2022; 11(3): 86-98. <https://doi.org/10.1007/s13665-022-00290-w>
14. Flaherty KR, Wells AU, Cottin V, Devaraj A, Walsh SLF, Inoue Y, et al. Nintedanib in Progressive Fibrosing Interstitial Lung Diseases. *N Engl J Med* 2019; 381(18): 1718-27. <https://doi.org/10.1056/NEJMoa1908681>
15. Allanore Y, Vonk MC, Distler O, Azuma A, Mayes MD, James A, et al. Continued nintedanib in patients with systemic sclerosis-associated interstitial lung disease: 3-year data from SENSICIS-ON. *RMD Open* 2025; 11(1). <https://doi.org/10.1136/rmdopen-2024-005086>
16. Khanna D, Maher TM, Volkmann ER, Allanore Y, Smith V, Assassi S, et al. Effect of nintedanib in patients with systemic sclerosis-associated interstitial lung disease and risk factors for rapid progression. *RMD Open* 2023; 9(1). <https://doi.org/10.1136/rmdopen-2022-002859>
17. Degirmenci G, Satıcı C, Azaklı Yazıcı D, Cetinkaya N, Erdem U, Demirkol B, et al. Comparison of the effectiveness of pirfenidone and nintedanib in patients with advanced stage idiopathic pulmonary fibrosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2025; 42(3): 16849.
18. Misirci S, Ekin A, Yagiz B, Coskun BN, Basibuyuk F, Birlik AM, et al. Treatment with nintedanib is as effective and safe in patients with other connective tissue diseases (CTDs)-interstitial lung disease (ILD) as in patients with systemic sclerosis-ILD: A multicenter retrospective study. *Clin Rheumatol* 2025; 44(3): 1187-95. <https://doi.org/10.1007/s10067-025-07323-0>
19. Ushio Y, Wakiya R, Kameda T, Nakashima S, Shimada H, Miyagi T, et al. Nintedanib combined with immunosuppressive agents improves forced vital capacity in connective tissue disease-associated PF-ILD: A single-center study. *BMC Rheumatol* 2024; 8(1): 27. <https://doi.org/10.1186/s41927-024-00400-y>
20. Namas R, Al Qassimi S, Elarabi M, Khan S, Almarzooqi A, Mubashir A, et al. Real-world Outcomes and Tolerability of Nintedanib in Patients With Systemic Autoimmune Rheumatic Disease-associated Interstitial Lung Disease: A Retrospective Study From a Single Center in a Middle Eastern Population. *J Clin Rheumatol* 2025. <https://doi.org/10.1097/RHU.0000000000002281>
21. Kuwana M, Allanore Y, Denton CP, Distler JHW, Steen V, Khanna D, et al. Nintedanib in Patients With Systemic Sclerosis-Associated Interstitial Lung Disease: Subgroup Analyses by Autoantibody Status and Modified Rodnan Skin Thickness Score. *Arthritis Rheumatol* 2022; 74(3): 518-26. <https://doi.org/10.1002/art.41965>
22. Boutel M, Boutou A, Pitsiou G, Garyfallos A, Dimitroulas T. Efficacy and Safety of Nintedanib in Patients with Connective Tissue Disease-Interstitial Lung Disease (CTD-ILD): A Real-World Single Center Experience. *Diagnostics (Basel)* 2023; 13(7). <https://doi.org/10.3390/diagnostics13071221>
23. Nakamura T, Jinta T, Kitamura A, Tanaka M, So C, Ro S, et al. Differences in Tolerability of Antifibrotic Agents Between Connective Tissue Disease-Associated and Non-connective Tissue Disease-Associated Interstitial Lung Disease. *Cureus* 2025; 17(2): e78750. <https://doi.org/10.7759/cureus.78750>
24. Arshad HME, Ali F, Babar A, Raza MZ, Maqsood M, Ameer A. Survival impact and safety comparison of pirfenidone and nintedanib for idiopathic pulmonary fibrosis: A meta-analysis. *Sarcoidosis Vasc Diffuse Lung Dis* 2025; 42(3): 16432.

25. Yang M, Wu Y, Liu X, Zhao C, Li T, Li T, et al. Efficacy and safety of antifibrotic agents in the treatment of CTD-ILD and RA-ILD: A systematic review and meta-analysis. *Respir Med* 2023; 216: 107329. <https://doi.org/10.1016/j.rmed.2023.107329>
26. Jee AS, Corte TJ. Current and Emerging Drug Therapies for Connective Tissue Disease-Interstitial Lung Disease (CTD-ILD). *Drugs* 2019; 79(14): 1511-28. <https://doi.org/10.1007/s40265-019-01178-x>
27. Maher TM. Interstitial Lung Disease: A Review. *JAMA* 2024; 331(19): 1655-65. <https://doi.org/10.1001/jama.2024.3669>
28. Weng C, Zhou Y, Zhang L, Wang G, Ding Z, Xue L, et al. Efficacy and safety of pharmacological treatments for autoimmune disease-associated interstitial lung disease: A systematic review and network meta-analysis. *Semin Arthritis Rheum* 2024; 68: 152500. <https://doi.org/10.1016/j.semarthrit.2024.152500>
29. Wells AU. New insights into the treatment of CTD-ILD. *Nat Rev Rheumatol* 2021; 17(2): 79-80. <https://doi.org/10.1038/s41584-020-00567-x>