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Nintedanib for progressive pulmonary fibrosis in real-world setting: an observational study comparing outcomes with an IPF cohort

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Abstract

Introduction Progressive Pulmonary Fibrosis (PPF) includes various fibrosing ILDs evolving similarly to Idiopathic Pulmonary Fibrosis (IPF). Nintedanib, previously approved for IPF, showed antifibrotic efficacy in PPF, but real-world data remain limited. This retrospective study investigated the real-world effectiveness of nintedanib in PPF compared to IPF, focusing on PFTs trends, tolerability, and impact of concomitant therapies.

Methods Data were retrospectively collected from an Italian referral centre (March 2021–August 2024). Study cohort met PPF classification criteria, while consecutive IPF patients were enrolled as control group. Lung function data at baseline, 12-months pre- and 12-month post-treatment were analysed using Linear Mixed Models. Adverse events and dose adjustments were recorded to assess safety.

Results Eighty-two PPF patients and 85 with IPF were included. At treatment initiation, the PPF group had significantly lower FVC (2.04 L vs 2.63 L; $p < 0.001$) and DLCO (46.41% vs 55.98%; $p = 0.002$), indicating more advanced disease. Nintedanib significantly reduced PPF cohort's FVC decline (–141.40 mL before treatment then –20.36 mL; $p < 0.001$). A sub-analysis in PPF patient with radiological UIP/UIPp pattern revealed an increased efficacy of antifibrotic treatment. Although IPF group had better baseline condition, they showed higher rate of lung function decline. Most PPF patients (81.7%) received concurrently immunomodulatory drugs. Adverse events were primarily gastrointestinal in both groups, with similar incidence of dose reductions and treatment discontinuation.

Conclusion In a real-world setting, nintedanib significantly slowed disease progression in PPF patients, mirroring outcomes and tolerability profile demonstrated in IPF. Further large-scale, prospective studies are needed to understand how to optimize antifibrotic therapy for PPF.

Keywords Progressive Pulmonary Fibrosis, Idiopathic Pulmonary Fibrosis, Antifibrotic drugs, Real-life study

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Introduction

Interstitial lung diseases (ILDs) comprise a broad and heterogeneous group of more than 200 conditions with variable clinical course and outcomes [1]. Idiopathic pulmonary fibrosis (IPF) is the paradigmatic model of fibrosing ILD, characterised by relentless progression of fibrosis and poor prognosis [2]. However, an estimated 13–40% of other ILDs may adopt a similar behaviour, developing a progressive fibrosing phenotype characterised by worsening respiratory symptoms, accelerated functional decline, and increasing fibrosis on imaging [3].

In 2022, the ATS/ERS/JRS/ALAT Clinical Practice Guideline formally defined the clinical, functional and radiological features of this phenotype, introducing the term Progressive Pulmonary Fibrosis (PPF) [4]. In patients with ILD of known or unknown aetiology, other than IPF, and radiological evidence of pulmonary fibrosis, PPF is defined by at least two of the following three criteria, occurring within the previous 12 months and not attributable to an alternative cause: 1) Worsening respiratory symptoms; 2) Physiological evidence of disease progression, defined as an absolute decline in FVC ≥ 5% predicted or an absolute decline in DLCO ≥ 10% predicted, within one year of follow-up; 3) Radiological evidence of disease progression, defined as increased extent or severity of traction bronchiectasis and bronchiolectasis, new ground-glass opacities with traction bronchiectasis, new fine reticulation, increased extent or coarseness of reticular abnormality, new or increased honeycombing, or increased lobar volume loss.

PPF therefore represents an umbrella term encompassing fibrosing ILDs with a trajectory reminiscent of IPF [5]. This includes entities secondary to known causes, such as connective tissue disease–associated ILD (CTD-ILD) [6], fibrotic hypersensitivity pneumonitis (fHP) [7] and sarcoidosis [8], as well as ILDs of unclear aetiology, such as idiopathic non-specific interstitial pneumonia (iNSIP) [9]. For this reason, PPF is a critical clinical endpoint because it can progress relentlessly despite conventional therapy, which typically includes corticosteroids and immunomodulatory drugs, alone or in combination [10].

Given the clinical and pathophysiological overlap between IPF and PPF, recent research has focused on shared biological pathways and common therapeutic approaches. Antifibrotic therapy for IPF is currently limited to Nintedanib and Pirfenidone, the only molecules that have demonstrated efficacy in slowing disease progression over the past decade [11, 12], while several other investigational compounds have failed to meet primary endpoints [13]. Among non-IPF fibrotic ILDs, the INBUILD trial was the first phase III randomised controlled trial (RCT) to demonstrate that nintedanib, a multi-target tyrosine kinase inhibitor [14], significantly slows the rate of lung function decline across a range of PPF phenotypes [15]. Based on these findings, the indication for nintedanib was extended to progressive fibrosing ILDs and incorporated into the 2022 guidelines as a treatment option for PPF patients who have failed standard management for the underlying ILD [4].

While RCTs provide high-level evidence for efficacy, real-world data are essential to understand how nintedanib performs in broader clinical practice, where ILD subtype, disease severity, concomitant medications and comorbidities may influence outcomes. A few real-world studies have suggested a favourable tolerability and effectiveness profile for nintedanib in PPF [16]. Nevertheless, these studies emphasized the need for further research to clarify its safety and efficacy across heterogeneous ILD populations outside the highly selected context of RCTs, a recurrent theme in respiratory medicine [17].

Accordingly, this study provides additional real-world evidence on nintedanib use in PPF. Its main novelty, not previously addressed in real-life studies, lies in the comparison of this cohort with a control group of patients with IPF, enabling assessment of differences in terms of the treated population, disease trajectory, and drug tolerability.

Methods

Study design

This was a retrospective, observational, case–control study. Data were collected from the clinical database of the Regional Referral Centre for Interstitial and Rare Lung Diseases of the University Hospital "G. Rodolico" of Catania, covering the period from March 2021 to August 2024. The study was conducted according to the Declaration of Helsinki and approved by our local ethical committee "Catania 1", (n°17/2023/0063184—November 13th, 2023). Informed consent was waived due to the retrospective use and anonymization of the data obtained from all patients.

Inclusion/exclusion criteria

Patients included in the PPF cohort were consecutively identified from our ILD clinic and institutional database during the study period. All cases were diagnosed with non-IPF fibrosing ILD and discussed in a multidisciplinary meeting (MDM) and considered eligible for Nintedanib initiation satisfying the PPF/PF-ILD criteria proposed in the INBUILD trial[15] over the preceding 24 months. These criteria are applied for Nintedanib prescription and reimbursement by Italian the National Health System):

- relative decline in FVC ≥ 10%

- Relative decline in FVC of 5%–10% with worsening respiratory symptoms or increased extent of fibrosis on HRCT scan.
- Worsening respiratory symptoms and increased extent of fibrosis on HRCT.

In addition, all patients were required to concomitantly meet the PPF classification criteria proposed by the 2022 ATS/ERS/JRS/ALAT guideline [4].

For the IPF control cohort, we selected patients from existing medical records who were diagnosed according to the 2022 updated guidelines [4] and who initiated Nintedanib treatment, according to the eligibility criteria for its prescription, between March 2021 and August 2024.

For both cohorts, we excluded patients with a follow-up period shorter than 12 months, antifibrotic treatment duration ≤ 3 months, unavailable functional data and > 10% of missing data.

Data collection

Data collected for both cohorts included sex, age at diagnosis, smoking status, Forced Vital Capacity (FVC), diffusing lung capacity for carbon monoxide (DLCO), 6 min walking test distance (6MWTD) at three different timepoints to assess the rate of decline before and after antifibrotic initiation: 1) 12 ± 6 months before starting treatment with Nintedanib, 2) at treatment initiation (baseline), 3) 12 ± 6 months after the initiation of treatment. Moreover, we reviewed clinical records to collect underlying ILD diagnosis, HRCT pattern at the time of Nintedanib initiation, occurrence of adverse events, including dose reduction, temporary suspension and definitive suspension. All patients underwent clinical assessment every 4–6 months. For both cohorts, use of oxygen therapy was categorised according to indication as exertional/ambulatory, nocturnal or long-term, and, when clinically evident, we recorded whether respiratory failure was deemed primarily related to concomitant pulmonary hypertension rather than ILD. Diagnosis was obtained according to the most recent guidelines or classification criteria for each condition and confirmed through multidisciplinary discussion (MDD), including pulmonologists, a rheumatologist (G.S) and a radiologist with high expertise in ILDs (S.P.).

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA). Continuous variables are reported as mean ± standard deviation (SD) and categorical variables as counts and percentages. Normality was assessed with the Shapiro–Wilk test. Between-group comparisons at baseline were performed using the independent-samples t-test or Mann–Whitney U-test for continuous variables, and the chi-squared test or Fisher's exact test for categorical variables, as appropriate.

To analyse longitudinal changes in pulmonary function and estimate the rate of decline before and after nintedanib initiation, we fitted linear mixed-effects models with a random intercept for subject, restricted linear splines were used to compare rate of change in the pre- and post nintedanib initiation periods. Fixed effects included time, treatment period (pre vs post), and their interaction. Pre- and post-treatment slopes were compared using model-based Wald tests, and results are presented as estimated slopes with 95% confidence intervals (95% CI) and p-values. The model was adjusted for age and sex. Two-sided p-values < 0.05 were considered statistically significant.

Results

Based on the proposed inclusion and exclusion criteria, 93 patients classified as PPF and eligible to start treatment with nintedanib were initially identified. The final study cohort comprised 82 individuals, after excluding 2 patients who declined antifibrotic therapy, 3 with > 10% missing data, and 6 who did not meet both sets of PPF/PF-ILD criteria (Fig. 1). The IPF control cohort included 85 patients who received a diagnosis of IPF and initiated nintedanib in the same time frame used for enrolment of the PPF group. In the PPF cohort, mean age was 71.24 ± 7.02 years, whereas the sex distribution was 39 (47,6%) females and 43 (47.6%) males. In the PPF cohort, mean age was 71.24 ± 7.02 years, and 39 (47.6%) patients were female and 43 (52.4%) male. In the IPF cohort, mean age was 70.17 ± 8.88 years (no significant difference vs PPF), with 70 (82.4%) males and 15 (17.6%) females. Smoking history, smoking exposure and mean duration of follow-up were similar between groups.

At nintedanib initiation, 62 (75.6%) patients in the PPF group were receiving supplemental oxygen, significantly more than in the IPF group (23 patients, 27.1%; $p < 0.001$). Among these patients, the majority in both cohorts were prescribed ambulatory oxygen therapy for exertional hypoxaemia (80.6% in the PPF group and 78.23% in the IPF group), based on documented desaturation ($SpO_2 < 90\%$) during 6MWT. In the PPF cohort, oxygen was considered primarily related to pulmonary hypertension rather than ILD in 4 cases, whereas this was not observed in any subjects of the IPF group. Demographic characteristics, use of oxygen therapy and mortality are reported in Table 1.

The PPF group encompassed a wide range of underlying ILD diagnoses. The most frequent diagnosis was iNSIP ($n = 21$, 25.6%), followed by rheumatoid arthritis–associated ILD (RA-ILD; $n = 16$, 19.5%), contributing to a

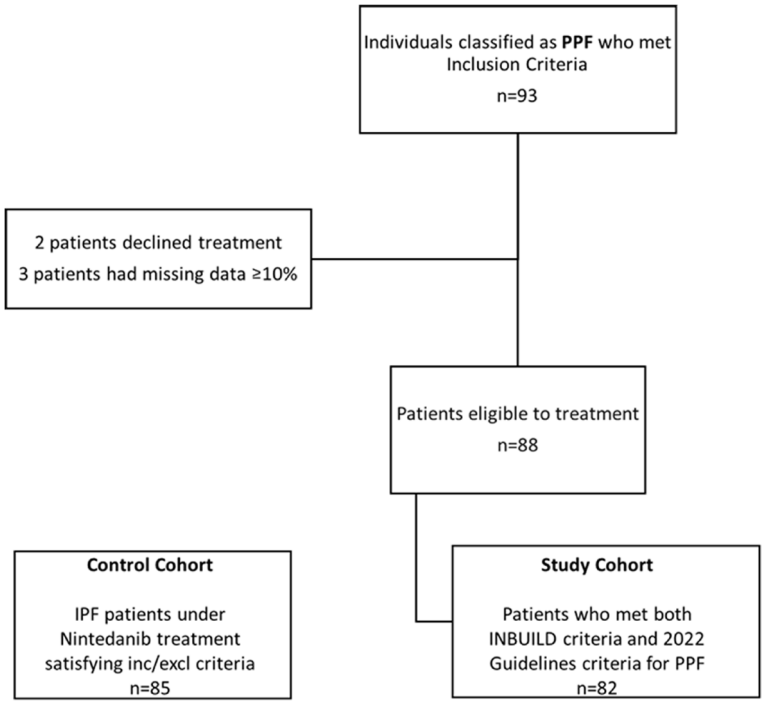

Fig. 1 Design of the study and recruitment of study and control cohort

Table 1 Characteristics of PPF and IPF cohort at initiation of treatment and occurrence of death during follow-up

	PPF (*n* = 82)	IPF (*n* = 85)	*p*-value
Age	71.24 ± 7.02	70.17 ± 8.88	0.68
Sex	M 43 (52.4%) F 39 (47.6%)	M 70 (82.4%) F 15 (17.6%)	< 0.001
BMI	28.76 ± 4.76	26.52 ± 3.17	0.001
Smoking history	Never 28 (34.1%) Former 53 (64.6%) Current 1 (1.2%)	Never 23 (27.1%) Former 58 (68.2%) Current 4 (4.7%)	0.29
Mean Smoking exposure (P-Y)	32.47 ± 25.86	40.87 ± 30.52	0.09
Mean time of Follow- up (months)	18.49 ± 8.36	18.24 ± 7.27	0.88
Time from diagnosis to study inclusion (months)	14.15 ± 8.91	7.71 ± 9.49	< 0.001
Supplemental Oxygen therapy at start of treatment	62 (75.6%)	23 (27.1%)	< 0.001
Deaths	3 (3.6%)	7 (8.2%)	0.21

PPF progressive pulmonary fibrosis, *IPF* idiopathic pulmonary fibrosis, *BMI* body mass index, *P-Y* pack-years

total of 36 patients (43.1%) with CTD-ILD. The distribution of underlying conditions is shown in Fig. 2A.

At the time of nintedanib initiation, the most common HRCT pattern in the PPF cohort was fibrotic NSIP ($n = 50$, 61.0%), followed by UIP ($n = 19$, 23.2%). When UIP and probable UIP ($n = 6$, 7.3%) were considered together, they accounted for almost one third of the cohort (Fig. 2B). In terms of background therapy, PPF patients received various immunosuppressive regimens according to the underlying diagnosis: corticosteroids (CCS, defined as ≥ 10 mg/day of prednisone or equivalent) were the most frequently used agents ($n = 67$, 81.7%), followed by mycophenolate mofetil ($n = 25$, 30.5%). More than half of the cohort ($n = 44$, 53.7%) were receiving two or more immunosuppressive drugs at baseline. The distribution of immunosuppressive treatments is reported in Supplementary Materials, Figure S1.

Regarding lung function, mean FVC at nintedanib initiation was 2.04 ± 0.81 L in the PPF cohort, significantly lower than in the IPF group (2.63 ± 0.84 L; $p < 0.001$). In PPF, the rate of FVC decline before nintedanib was −141.40 mL/year (95% CI −217.07 to −65.73), which was significantly reduced to −20.36 mL/year (95% CI −59.61 to 18.88; $p < 0.001$) after treatment initiation (Fig. 3A). Percent predicted FVC (ppFVC) and DLCO at baseline were also significantly lower in PPF than in IPF (ppFVC 69.05 ± 20.56%, 95% CI 64.31–73.78 vs 81.28 ± 18.98%, 95% CI 76.68–85.88; $p < 0.001$; DLCO 46.41 ± 15.51%, 95% CI 43.18–49.63 vs 55.98 ± 19.95%, 95% CI 51.62–60.34; $p = 0.002$). However, no statistically significant differences were observed in the rate of change of ppFVC or DLCO before and after nintedanib (Figs. 3B and 3C). In contrast, 6MWTD decline in the PPF cohort showed a numerically greater reduction after nintedanib initiation (−20.30 m/year vs −61.09 m/year), but this difference did not reach statistical significance ($p = 0.216$; Fig. 3D).

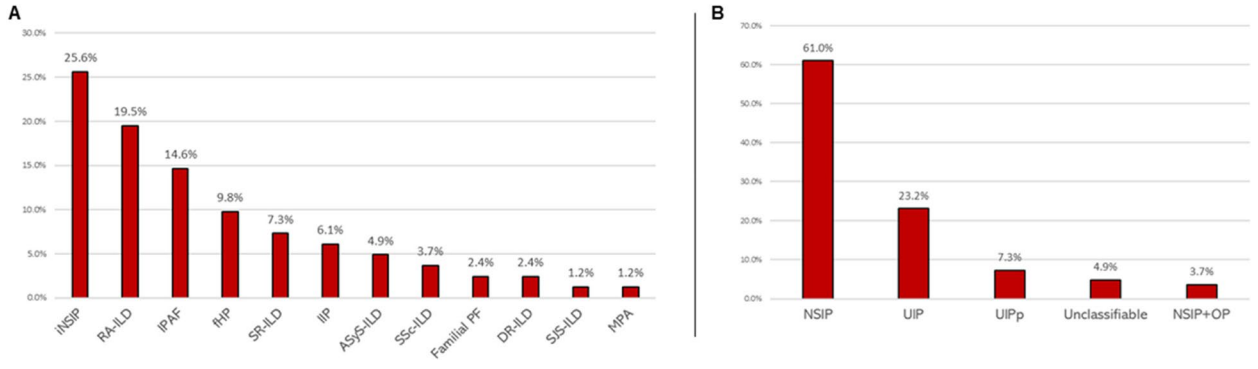

Fig. 2 **A** Underlying conditions of the PPF Cohort. **B** Radiological pattern distribution at initiation of treatment in the PPF cohort. iNSIP: idiopathic nonspecific interstitial pneumonia; RA-ILD: rheumatoid arthritis-associated interstitial lung disease; IPAF: interstitial pneumonia with autoimmune features; fHP: fibrosing hypersensitivity pneumonitis; SR-ILD: smoking related-interstitial lung disease; IIP: idiopathic interstitial pneumonia; ASyS-ILD: antisynthetase syndrome-associated interstitial lung disease; SSc-ILD: systemic sclerosis-associated interstitial lung disease; Familial PF: familial pulmonary fibrosis; DR-ILD: drug related interstitial lung diseases; SjS-ILD: Sjogren's Syndrome associated interstitial lung diseases; MPA: microscopic polyangiitis. NSIP: nonspecific interstitial pneumonia; UIP: usual interstitial pneumonia; UIPp: probable usual interstitial pneumonia; NSIP + OP: nonspecific interstitial pneumonia and organizing pneumonia

In the IPF cohort, disease trajectories showed similar trends with some differences: the reduction in FVC decline after nintedanib was less pronounced than in PPF (−99.30 mL/year pre-treatment vs −89.35 mL/year post-treatment; $p = 0.89$). Conversely, the decline in ppDLCO decreased (−8.58% vs −3.29%; $p = 0.27$), while 6MWTD remained essentially stable (−13.90 m vs −16.96 m; $p = 0.94$). IPF plots for each variable are presented in Supplementary Material, Figure S2. Mean lung function values at each timepoint for both cohorts are reported in Table 2, and the comparison of rates of change for each variable is summarised in Table 3.

The same longitudinal analysis was also performed in a subgroup of PPF patients whose HRCT pattern was either UIP or UIP probable ($n = 25$). In this subgroup, nintedanib significantly reduced the decline in FVC, both in absolute terms and as percent predicted: FVC decreased from −274.23 mL/year before treatment to −3.42 mL/year after treatment ($p = 0.015$), and ppFVC from −6.87% to −0.99% per year ($p = 0.038$). Consistent with these findings, the decline in ppDLCO slowed from −8.09% to −2.85% per year, although this difference did not reach statistical significance ($p = 0.39$). As in the overall PPF cohort, 6MWTD in the UIP/UIP-probable subgroup showed a modest further reduction over time (−34.17 m vs −46.17 m/year before and after treatment, respectively). Lung function values and corresponding rates of change for this subgroup are shown in Fig. 4 and detailed in Supplementary Materials, Table S1.

The overall incidence of adverse events (AEs) was similar in the two cohorts (Fig. 5), with higher rate in IPF ($n = 62$, 73.8%) than in PPF ($n = 52$, 63.4%; $p = 0.14$). Diarrhoea was the most common AE in both groups (50.6% in IPF and 48.8% in PPF; $p = 0.39$). Nausea and vomiting were more frequent in IPF (21.9% vs 14.1%; $p = 0.086$), whereas weight loss (17.6% vs 9.7%; $p = 0.22$) and increased liver enzymes (19.5% vs 15.3%; $p = 0.36$) occurred more often, though not significantly, in PPF. The proportion of patients experiencing AEs leading to dose reduction or treatment interruption was comparable (26.8% in IPF vs 21.2% in PPF; $p = 0.39$), with diarrhoea and liver enzyme elevation as the main causes. During follow-up, 3 patients (3.6%) in the PPF cohort and 7 (8.2%) in the IPF cohort died, with no statistically significant difference between groups ($p = 0.21$).

Discussion

This research highlighted that, in a real-world context, the decline in lung function among patients with non-IPF progressive pulmonary fibrosis (PPF) was significantly attenuated over 12 months following nintedanib initiation. Compared with previously published real-life cohorts, our work adds a distinctive perspective by including a parallel IPF cohort, allowing a more nuanced comparison of disease trajectories and treatment timing. This side-by-side evaluation underscores how PPF and IPF differ in real-world therapeutic practice, particularly regarding the stage of disease at which antifibrotic therapy is initiated—an issue that has long been central in the IPF field [18].

At baseline, the PPF cohort had markedly lower FVC and DLCO than the IPF cohort, indicating more advanced functional impairment at the time of nintedanib initiation. Despite this, after treatment the PPF group experienced a greater reduction in the rate of FVC decline than the IPF group. This finding may reflect, at least in part, optimisation of background immunomodulatory therapy—given that most PPF patients received at least one concomitant immunosuppressive agent—as well as the intrinsically poorer prognosis typically

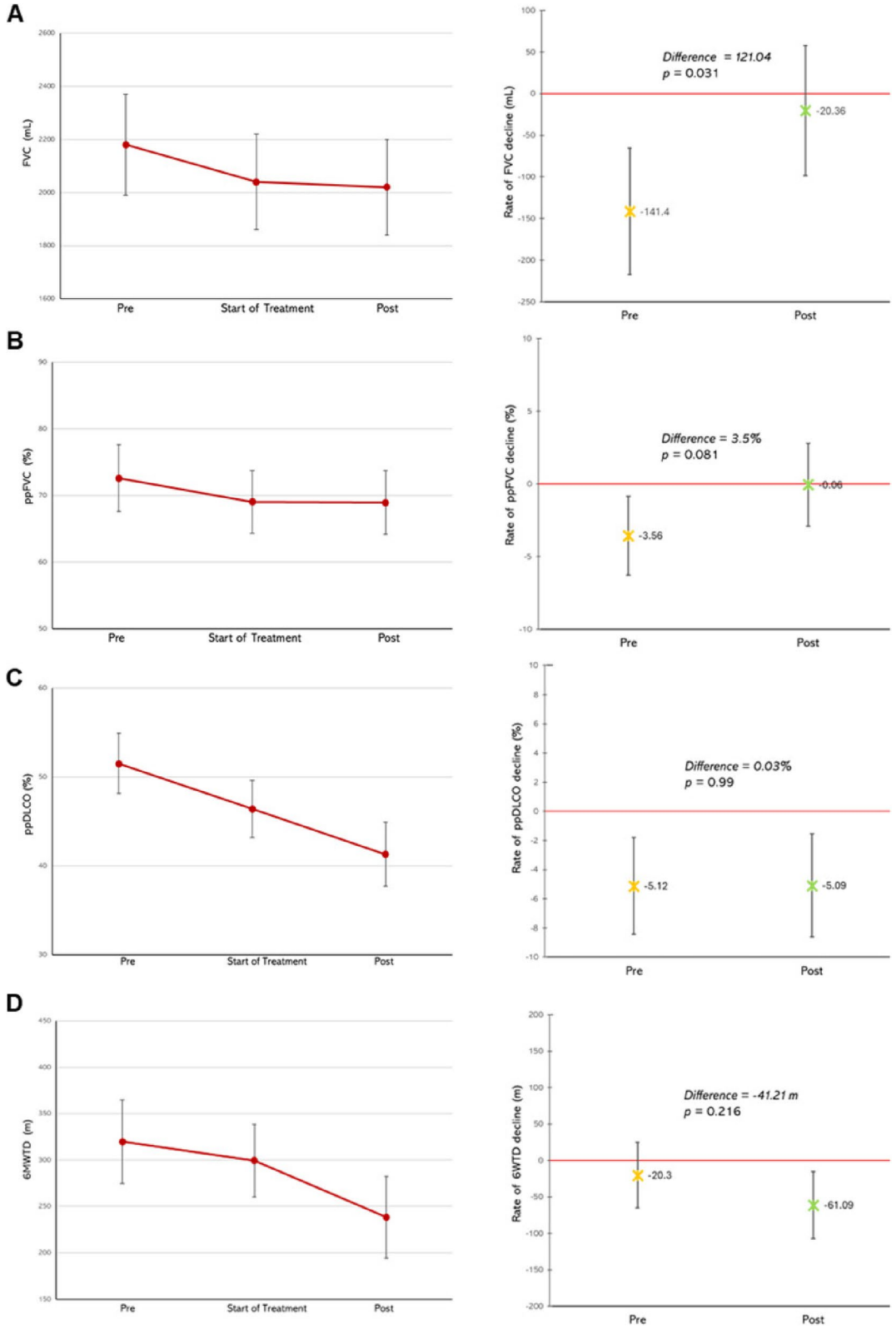

Fig. 3 Mean values at each timepoint and estimated rate of decline before and after nintedanib initiation in the PPF cohort for: (**A**) FVC (mL); (**B**) ppFVC (% predicted); (**C**) DLCO (% predicted); and (**D**) 6MWTD (m). The rates of decline were estimated using unadjusted linear mixed-effects models with a random intercept for patient, and pre- vs post-treatment rates were compared using Wald tests. FVC: Forced Vital Capacity; ppFVC: percent predicted FVC; DLCO: diffusing lung capacity for carbon monoxide; 6MWTD: 6 min walking test distance

Table 2 Lung function at pre-initiation (−12 ± 6 months), start of treatment and post-initiation (+ 12 ± 6 months) for study groups

	Pre-initiation (−12 ± 6 months)			Start of treatment			Post-initiation (+ 12 ± 6 months)		
	PPF	IPF	*p*-value	PPF	IPF	*p*-value	PPF	IPF	*p*-value
	(*n* = 82)	(*n* = 85)		(*n* = 82)	(*n* = 85)		(*n* = 82)	(*n* = 85)	
FVC (L)	2.18 ± 0.84 (95%CI 1.99–2.36)	2.73 ± 0.89 (95%CI 2.53–2.92)	0.012	2.04 ± 0.81 (95%CI 1.85–2.22)	2.63 ± 0.84 (95%CI 2.45–2.82)	< 0.001	2.02 ± 0.87 (95%CI 1.83–2.20)	2.54 ± 0.89 (95%CI 2.36–2.73)	< 0.001
ppFVC (%)	72.60 ± 2 2.14 (95%CI 67.83–77.38)	83.18 ± 1 8.21 (95%CI 78.25–88.10)	0.01	69.05 ± 2 0.56 (95%CI 64.31–73.78)	81.28 ± 1 8.98 (95%CI 76.68–85.88)	< 0. 001	68.97 ± 2 2.20 (95%CI 64.12–73.85)	79.96 ± 22.22 (95%CI 75.29–84.64)	0.005
DLCO (%)	51.53 ± 15,21 (95%CI 48.19–54.87)	64.56 ± 21.83 (95%CI 59.78–69.32)	< 0.001	46.41 ± 15,51 (95%CI 43.18–49.63)	55.98 ± 19.95 (95%CI 51.62–60.34)	0.002	41.32 ± 13.26 (95%CI 37.72–44.91)	52.68 ± 17.70 (95%CI 48.28–57.09)	< 0.001
6M WTD (m)	319.70 ± 152.65 (95%CI 276.19–363.21)	375.25 ± 138.94 (95%CI 318.86–431.63)	0.08	299.40 ± 163.75 (95%CI 259.48–339.32)	365.07 ± 147.26 (95%CI 326.09–404.05)	0.03	238.32 ± 144.91 (95%CI 194.05–282.58)	345.98 ± 159,21 (95%CI 309.94–382.01)	0.01

Legend: *PPF* Progressive Pulmonary Fibrosis, *IPF* Idiopathic Pulmonary Fibrosis, *FVC* Forced Vital Capacity, *ppFVC* percent predicted FVC, *DLCO* diffusing lung capacity for carbon monoxide, *6MWTD* distance at the 6 min walking test

Table 3 Differences in lung function between period before treatment initiation and after start of treatment

	Rate of change		
PPF	PRE	POST	*p*-value
FVC (ml)	−141.40 (95%CI −217.07 to −65.73)	−20.36 (95%CI −100.33- −59.61)	0.031
ppFVC (%)	−3.56 (95%CI −6.29—−0.84)	−0.06 (95%CI −2.91- 2.79)	0.081
DLCO (%)	−5.12 (95%CI −8.44- −1.81)	−5.09 (95%CI −8.63- −1.54)	0.99
6MWTD (m)	−20.30 (95%CI −65.34–24.74)	−61.09 (95%CI −107.91- −14.26)	0.216
FVC (ml)	−99.30 (95%CI −206.39- 7.78)	−89.35 (95%CI −187.971- 9.26)	0.89
ppFVC (%)	−1.89 (CI95% −5.79- 2.01)	−1.32 (95%CI −4.90- 2.26)	0.83
DLCO (%)	−8.58 (95%CI −13.10- −4.06)	−3.29 (95%CI −7.37–0.78)	0.27
6MWTD (m)	−13.90 (95%CI −84.62–56.82)	−16.96 (95%CI −71.89–37.97)	0.94

Legend: *PPF* Progressive Pulmonary Fibrosis, *IPF* Idiopathic Pulmonary Fibrosis, *FVC* Forced Vital Capacity, *ppFVC* percent predicted FVC, *DLCO* diffusing lung capacity for carbon monoxide, *6MWTD* distance at the 6 min walking test

associated with IPF. Importantly, the apparent attenuation of FVC decline under nintedanib should also be interpreted in the context of the underlying disease trajectory: some PPF entities, particularly CTD-ILD, may follow a more indolent course. This is consistent with the multicentre study by Oldham et al., which demonstrated heterogeneous FVC trajectories across ILD subtypes after meeting PF-ILD criteria, with CTD-ILD generally showing a slower subsequent decline [19]. Our findings therefore likely reflect a combination of treatment effect and the intrinsic natural history of these diseases.

In our IPF cohort, baseline lung function values were consistent with mild-to-moderate disease. This may partly explain the slower pre-treatment decline compared with PPF and the magnitude of FVC decline observed under therapy, which was nevertheless comparable to that reported in the INPULSIS-1 and −2 trials [11] (−89.35 mL/year in our study vs −114.7 and −113.6 mL/year, respectively). The mechanisms underlying these differences are likely multifactorial and may involve disease biology, comorbidities and pharmacodynamic factors, warranting further study.

Of note, the subgroup analysis of PPF patients with a UIP/UIP-probable pattern yielded particularly striking results. Although limited by sample size, these data support the hypothesis that fibrosing ILDs with a UIP-like pattern may derive substantial benefit from antifibrotic therapy and suggest that prolonged observation to document formal progression might not always be necessary in the presence of a clearly fibrotic phenotype.

The marked reduction in FVC decline in the PPF group (from −141.4 mL/year pre-treatment to −20.36 mL/year after nintedanib) also raises the possibility that concomitant immunosuppressive regimens may enhance antifibrotic efficacy. Previous evidence, including the SENSCIS trial [20], has suggested a favorable interaction between nintedanib and immunomodulatory agents such as mycophenolate mofetil, without an increase in adverse events [21]. These findings underline the importance of disease subtype and background therapy when considering antifibrotic strategies. Personalising treatment according to individual disease characteristics, rather than adopting a uniform approach, may optimise outcomes and promote more tailored management of ILDs. Furthermore, after nearly a decade of unsuccessful trials of novel agents, phase 3 FIBRONEER-ILD and FIBRONEER-IPF randomized clinical trials have recently reported that Nerandomilast, an oral preferential phosphodiesterase-4B inhibitor, is effective in slowing lung function decline

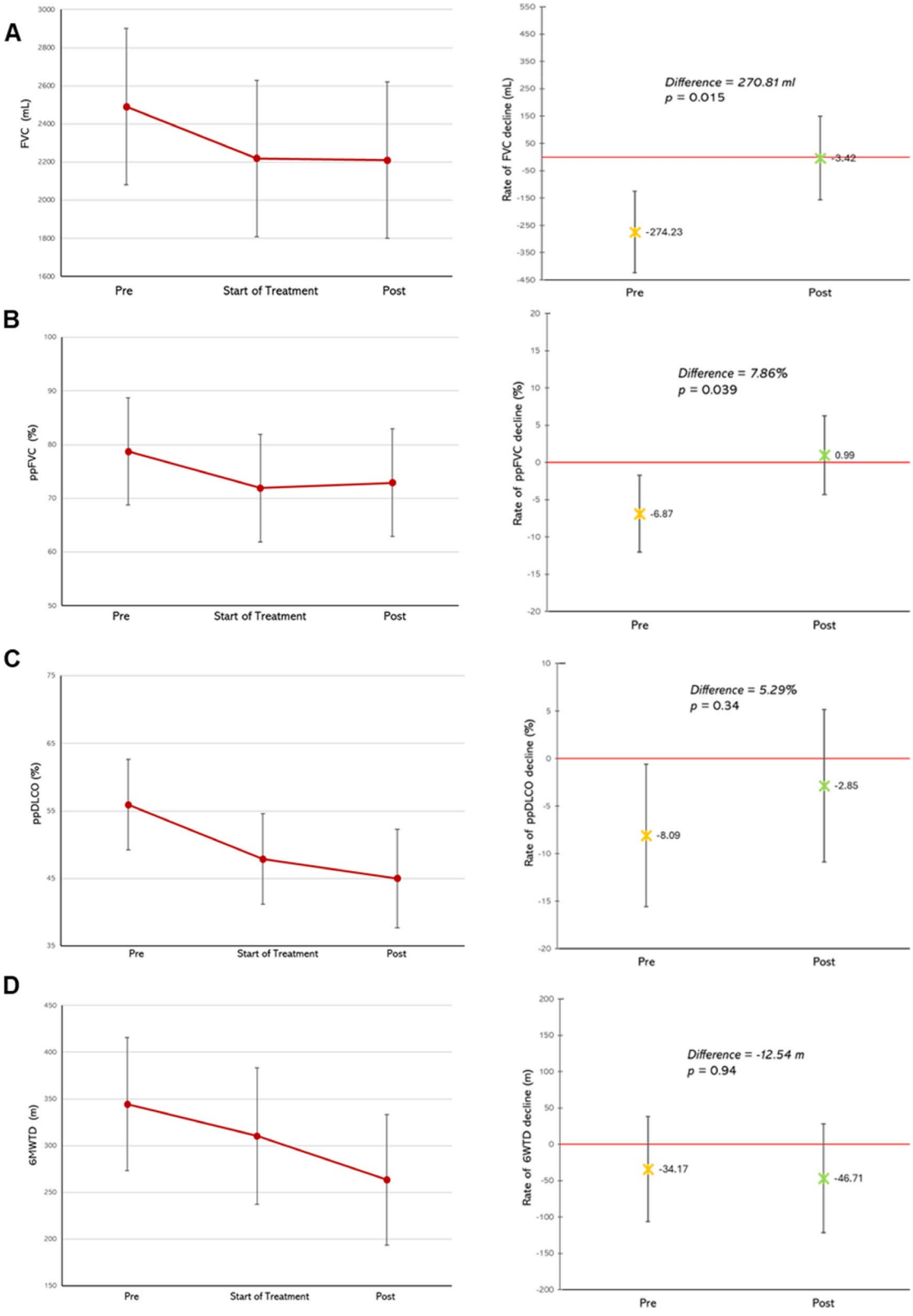

Fig. 4 Mean values at each timepoint and estimated rate of decline before and after nintedanib initiation in UIP/UIPp subgroup for: (**A**) FVC (mL); (**B**) ppFVC (% predicted); (**C**) DLCO (% predicted); and (**D**) 6MWTD (m). The rates of decline were estimated using unadjusted linear mixed-effects models with a random intercept for patient, and pre- vs post-treatment rates were compared using Wald tests. FVC: Forced Vital Capacity; ppFVC: percent predicted FVC; DLCO: diffusing lung capacity for carbon monoxide; 6MWTD: distance at the 6 min walking test

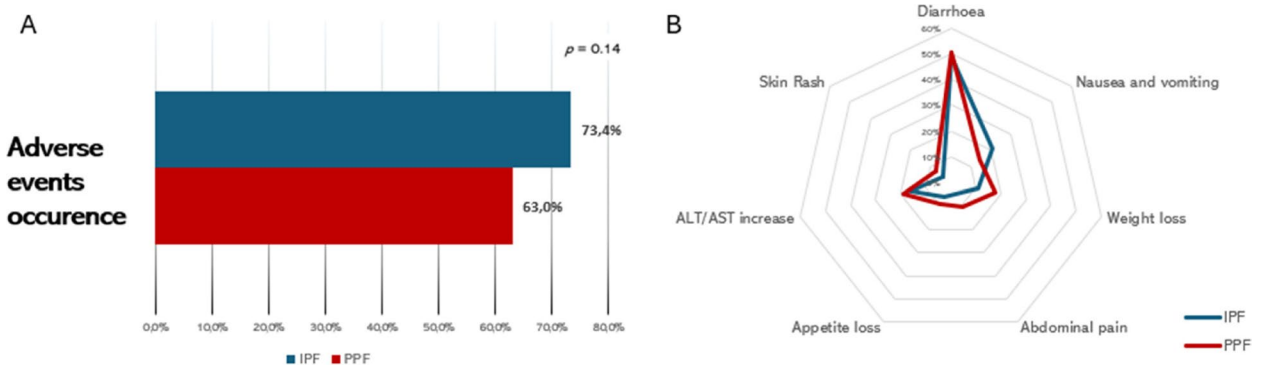

Fig. 5 **A** Proportion of individuals experiencing adverse events on antifibrotic treatment in IPF and PPF cohorts. **B** Incidence of most common Nintedanib adverse events in both groups. Legend: ALT: alanine aminotransferase; AST: Aspartate aminotransferase; IPF: Idiopathic Pulmonary Fibrosis; PPF: Progressive Pulmonary Fibrosis

in both PPF and IPF [22, 23]. Notably, subgroup analyses suggested excellent efficacy and tolerability in patients receiving background nintedanib, laying the foundation for future combination or add-on antifibrotic strategies.

In terms of safety, our study showed an acceptable tolerability profile for nintedanib in PPF, comparable to that observed in IPF, and confirmed gastrointestinal events as the most frequent AEs, consistent with a meta-analysis including the INBUILD trial and its post hoc analyses [24]. Importantly, the overall discontinuation rate in our cohort (18%) was lower than in previously reported UK real-world data (26–30%) [25], suggesting good adherence to therapy even in patients receiving concomitant immunosuppression.

Our findings are broadly consistent with the large real-world study by Raman et al., which currently represents the most extensive evaluation of nintedanib in PPF [16]. Despite methodological differences, the post-treatment FVC trajectory was similar (−151.2 mL/year vs −121.04 mL/year in our analysis). Raman and colleagues conducted a multicentre study within an early-access programme, including patients with more advanced disease who initiated nintedanib only after fulfilling PF-ILD criteria derived from INBUILD [15]. In contrast, our monocentric cohort reflects prescribing regulations of the Italian National Health Service and included patients meeting both INBUILD and 2022 guideline criteria [4]. Nevertheless, the convergence of results across distinct settings reinforces the real-life effectiveness of nintedanib for PPF.

This study has several limitations. Its retrospective design and relatively small sample size are closely linked to the limited observation period and monocentric nature of the cohort. In addition, the distribution of ILD subtypes likely reflects centre-specific referral patterns, with SSc-ILD cases being predominantly managed within rheumatology-led pathways in our region. The longer time from diagnosis to nintedanib initiation in PPF also suggests possible survival bias, potentially favoring the inclusion of patients with more indolent trajectories. Nonetheless, the study has important strengths. To our knowledge, it represents the first Italian real-world analysis including a heterogeneous cohort spanning the spectrum of PPF, and the first to directly compare PPF and IPF trajectories before and after nintedanib initiation. This comparative framework highlights practical considerations regarding disease stage and timing of antifibrotic initiation. Moreover, the IPF comparison allowed a more refined assessment of disease behavior and contributed to clarifying key aspects of antifibrotic management in this complex group of disorders, including the role of concomitant therapies.

Conclusion

In conclusion, our findings confirm the therapeutic benefit of nintedanib in patients with PPF, likely driven by the combined effect of antifibrotic and immunosuppressive treatments. By integrating real-world data from a heterogeneous cohort, this study provides additional insight into the practical benefits and challenges of nintedanib therapy, which is crucial for optimising management strategies in non-IPF fibrotic ILDs. The apparent efficacy of nintedanib in PPF with a clearly fibrotic pattern may prompt reconsideration of the need to await documented progression before initiating antifibrotic therapy. Future prospective, large-scale studies are needed to confirm these hypotheses and to further elucidate shared pathogenic pathways between IPF and PPF, with the ultimate goal of identifying new effective agents and refining therapeutic strategies.

Abbreviations

6MWTD	6-Minute walking test distance
AEs	Adverse events
ASyS-ILD	Anti-synthetase syndrome-associated interstitial lung disease
BMI	Body mass index
CTD-ILD	Connective tissue disease-associated interstitial lung disease
DLCO	Diffusing capacity for carbon monoxide
DR-ILD	Drug related interstitial lung diseases
Familial PF	Familial pulmonary fibrosis
fHP	Fibrosing hypersensitivity pneumonitis
FVC	Forced Vital Capacity

HRCT	High-resolution computed tomography
IIP	Idiopathic interstitial pneumonia
ILD	Interstitial Lung Disease
iNSIP	Idiopathic nonspecific interstitial pneumonia
IPAF	Interstitial pneumonia with autoimmune features
IPF	Idiopathic Pulmonary Fibrosis
MDM	Multidisciplinary meeting
MPA	Microscopic polyangiitis
NSIP	Nonspecific interstitial pneumonia
NSIP + OP	Nonspecific interstitial pneumonia and organizing pneumonia
PPF	Progressive Pulmonary Fibrosis
ppFVC	Percent predicted Forced Vital Capacity
P-Y	Pack/years
RA-ILD	Rheumatoid arthritis-associated interstitial lung disease
SjS-ILD	Sjogren's Syndrome associated interstitial lung diseases
SR-ILD	Smoking related-interstitial lung disease
SSc-ILD	Systemic sclerosis-associated interstitial lung diseas
UIP	Usual interstitial pneumonia
UIPp	Probable usual interstitial pneumonia

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
Conceptualization, G.M., A.L., G.S. and C.V.; data curation, G.M., A.L., E.G., M.F. and S.M.; formal analysis, G.M., E.G., M.F., S.M. and S.P.; investigation, G.M., A.L., C.R. and G.S.; methodology, L.S. and C.V.; software, G.M.; supervision, S.P., L.S., G.S. and C.V.; validation, G.M., G.S. and C.V.; visualization, G.M., A.L., S.P. and G.S.; writing—original draft preparation, G.M. and C.R.; writing—review and editing, G.M., A.L., E.G., M.F., S.M., S.P., L.S., G.S., and C.V.. All authors have read and approved the final version of the manuscript.

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Data availability
The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author (G.M. – email: giuseppe.muscato@phd.unict.it) upon request.

Declarations

Ethics approval and consent to participate
The study was conducted according to the Declaration of Helsinki and approved by our local ethical committee "Catania 1" (n°17/2023/0063184—November 13th, 2023). Informed consent was waived due to the retrospective use and anonymization of the data obtained from all patients.

Consent for publication
Not applicable.

Competing interests
G. Muscato, A. Libra, C. Reina, E. Gili, M. Fruciano, S. Martella, L. Spicuzza and S. Palmucci have nothing to disclose. G. Sambataro reports honoraria for lectures from Boehringer Ingelheim, outside the submitted work. C. Vancheri reports grants from F. Hoffmann-La Roche, Boehringer Ingelheim and Astra Zeneca, and honoraria for lectures from F. Hoffmann-La Roche, Boehringer Ingelheim, Chiesi, Grifols, Menarini, and participation on an advisory board for F. Hoffmann-La Roche and Boehringer Ingelheim, outside the submitted work.

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