# Effect of nintedanib on acute exacerbations of fibrosing interstitial lung diseases: a national database study in Japan

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## Abstract

*Background* Acute exacerbation is a life-threatening event in patients with fibrosing interstitial lung diseases (ILDs). Although nintedanib reduces acute exacerbation incidence, its effectiveness during acute exacerbation is unclear.

*Methods* Using data from the Diagnosis Procedure Combination database (September 2015–March 2020) in Japan, we identified patients with fibrosing ILDs who received intravenous injection of high-dose corticosteroid within 3 days post-admission and analysed their first hospitalisation. We performed overlap propensity score weighting to compare in-hospital outcomes between patients who received nintedanib within 14 days post-admission and those who did not. The primary and secondary outcomes were in-hospital mortality and length of hospitalisation in the patients discharged alive, respectively.

*Results* Among the 6235 identified patients, 353 patients received nintedanib within 14 days post-admission. In-hospital mortality occurred in 13.7% and 6.0% patients in the control (n=5882) and nintedanib-treated (n=353) patients, respectively. The mean length of hospitalisation was 39.9 and 30.4 days in the control and nintedanib-treated patients, respectively. After overlap propensity score weighting, nintedanib treatment was significantly associated with lower in-hospital mortality in the adjusted cohort (OR 0.43, 95% CI 0.27–0.70; p=0.001). The mean length of hospitalisation in nintedanib-treated patients (30.7 days) was significantly shorter than that in the control group (37.5 days; p<0.001).

*Conclusions* Nintedanib initiation during acute exacerbation was significantly associated with a lower risk of in-hospital death and shorter length of hospitalisation in patients with fibrosing ILDs. Our results elucidate the potential role of nintedanib in the treatment of acute exacerbation in patients with fibrosing ILDs. Further prospective studies are warranted.

## Introduction

Acute exacerbation is a life-threatening event in patients with idiopathic pulmonary fibrosis (IPF) [1]. Acute exacerbations reportedly occur in IPF and in a wide range of fibrosing interstitial lung diseases (ILDs) [2].

Earlier studies suggested that nintedanib could reduce the incidence of acute exacerbations in fibrosing ILDs [3]. Recently, nintedanib was reported to inhibit IPF and fibrosing ILD progression, regardless of the

aetiology, and was prescribed to various patients with pulmonary fibrosis, under the disease concept of progressive fibrosing ILDs [4]. Thus, nintedanib is considered a key drug for treating fibrosing ILDs.

Considering acute exacerbation treatment, high-dose corticosteroids have been used empirically, particularly in Japan [5]. However, the effectiveness of high-dose corticosteroid has not been demonstrated [6]; thus, establishing an effective treatment for acute exacerbation in fibrosing ILDs is warranted. A recent survey reported that 67% of clinical pulmonologists initiated antifibrotic therapies as treatment for acute exacerbation in patients who had not previously received antifibrotic therapy [7]. However, the effectiveness of antifibrotic therapy for acute exacerbation in fibrosing ILDs, in contrast to its effectiveness in inhibiting acute exacerbation onset, has not been elucidated.

In this study, we examined the effectiveness of nintedanib initiation during the treatment of acute exacerbation in patients with fibrosing ILDs using a nationwide inpatient database in Japan.

## Materials and methods
### Data source
We conducted a retrospective cohort study using the Diagnosis Procedure Combination database [8], which is a national inpatient database in Japan. The database includes data on patient sex, age, body height and weight (body mass index), Charlson Comorbidity Index [9], smoking history (pack-years), Hugh-Jones dyspnoea scale scores [10], activities of daily living scores (Barthel index) [11], dates of admission and discharge, main diagnoses, comorbidities on admission, medications, information on assisted ventilation, and discharge status. The data of approximately 300 hospitals are combined with the outpatient data on the treatments and prescriptions.

This study was approved by the Institutional Review Board of The University of Tokyo (Tokyo, Japan). The review board waived the requirement for informed consent owing to the use of anonymised data.

### Patient selection
As nintedanib has been commercially available in Japan since September 2015, we collected data on patients who were admitted for the treatment of fibrosing ILDs, defined by International Classification of Diseases, 10th Revision (ICD-10) codes J841 and J848–J849, between September 2015 and March 2020. As the ICD-10 codes do not include specific codes for IPF, patients with IPF were further extracted using the diagnosis for IPF recorded in Japanese text. As high-dose corticosteroid intravenous injection treatment (*i.e.* 500 or 1000 mg methylprednisolone per day) is most commonly used for acute exacerbation treatment in Japan [5], we defined the onset of acute exacerbation as the receipt of this corticosteroid therapy within 3 days after admission. By using this definition, we expected to procure a homogenous patient population considering the severity of acute exacerbation in fibrosing ILDs. The first hospitalisation requiring corticosteroid therapy during the observation period was defined as the index hospitalisation and was analysed for each patient. For adjustment purposes, to evaluate the medications patients received before the index hospitalisation, we excluded patients who did not visit the hospital within 90 days prior to the index hospitalisation. We also excluded patients who received nintedanib prior to the index hospitalisation. Those who received pirfenidone, another antifibrotic drug, during the index hospitalisation were excluded in order to focus on the effect of nintedanib.

Patients who received mechanical ventilation with tracheal intubation or those who did not receive oral corticosteroids within 14 days following admission were also excluded. To account for immortal time bias, we excluded patients who died or were discharged within 14 days after admission. We defined patients who received nintedanib for the first time within 14 days after the index hospitalisation as the nintedanib group and the other patients as the control group.

### Covariates
To evaluate the differences in background patient characteristics, we compared the control and nintedanib groups using the following covariates at admission: sex, age, body mass index (categorised according to World Health Organization definitions into underweight (<18.5 kg·m$^{-2}$), normal weight (18.5–24.9 kg·m$^{-2}$), overweight (25.0–29.9 kg·m$^{-2}$) and obese (⩾30.0 kg·m$^{-2}$)), Charlson Comorbidity Index, smoking history (pack-years), severity of respiratory condition (Hugh-Jones dyspnoea scale), activities of daily living scores (Barthel index: fully independent (100), independent (60–95) and dependent (0–55)), date of admission, prescriptions of oral corticosteroid and pirfenidone prior to the index hospitalisation, main diagnoses (IPF or not), comorbidities on admission identified by recorded ICD-10 codes (respiratory failure (J96), bacterial pneumonia (J13–J18), COPDs (J41–J44), pneumothorax (J93), heart disease (I20–I25, I50, I110), liver disease (B15–B19, K70–K77), gastro-oesophageal reflux disease (GORD) (K21),

cancer (C00–C97), bronchial asthma (J45–J46), hypertension (I10–I13, I15), diabetes mellitus (E10–E14), thyroid diseases (E03–E06) and osteoporosis (M80–M82)), mean number of days from admission to *i.v.* injection of high-dose corticosteroid, use of noninvasive positive pressure ventilation, and mean number of admissions at the index hospitalisation.

## Study outcomes
The primary outcome of this study was in-hospital death. The secondary outcome was the length of hospital stay in patients who were discharged alive.

## Statistical analysis
Propensity score analysis can effectively adjust for measured confounders and is most commonly used to balance patient backgrounds between the two groups (treated and untreated) in retrospective studies [12]. The propensity score is defined as the probability of assigning an individual to the treatment group. In the present study, propensity scores for receiving nintedanib treatment were calculated using a multivariable logistic regression model containing all the aforementioned covariates. To attain adequate balance between bias and variance, we performed overlap propensity score weighting [13]. Overlap propensity score weights were defined as 1 minus the propensity scores for the nintedanib group and the propensity scores for the control group. Overlap propensity score weighting achieves an exact balance in measured variables and an accurate estimation of the association between treatment and outcome compared with conventional propensity score methods such as matching or inverse probability weighting [14]. The created patient population mimics the cohort of a randomised control trial without excluding patients from the original cohort. Baseline characteristics were compared between the two groups using the standardised mean difference before and after weighting, with an absolute standardised difference of <0.1 considered to denote a negligible difference in covariates [15]. In-hospital mortality was compared between the two groups using Fisher's exact test. Overlap propensity score-weighted logistic regression analyses were performed to estimate the odds ratio of in-hospital death and the 95% confidence interval between the two groups. Length of hospital stay was also analysed *via* linear regression analyses. All statistical analyses were performed using Stata version 17.0 (StataCorp, College Station, TX, USA). A two-tailed significance level of 0.05 was used in all statistical analyses.

## Subgroup and sensitivity analyses
We conducted subgroup analyses restricted to patients with IPF or non-IPF. Four sensitivity analyses were also conducted. For the first sensitivity analysis, we included patients with fibrosing ILDs who received an *i.v.* injection of high-dose corticosteroid within 10 days, instead of the 3 days in the main analysis, as those with acute exacerbation. For two other sensitivity analyses, we used an alternative definition of the



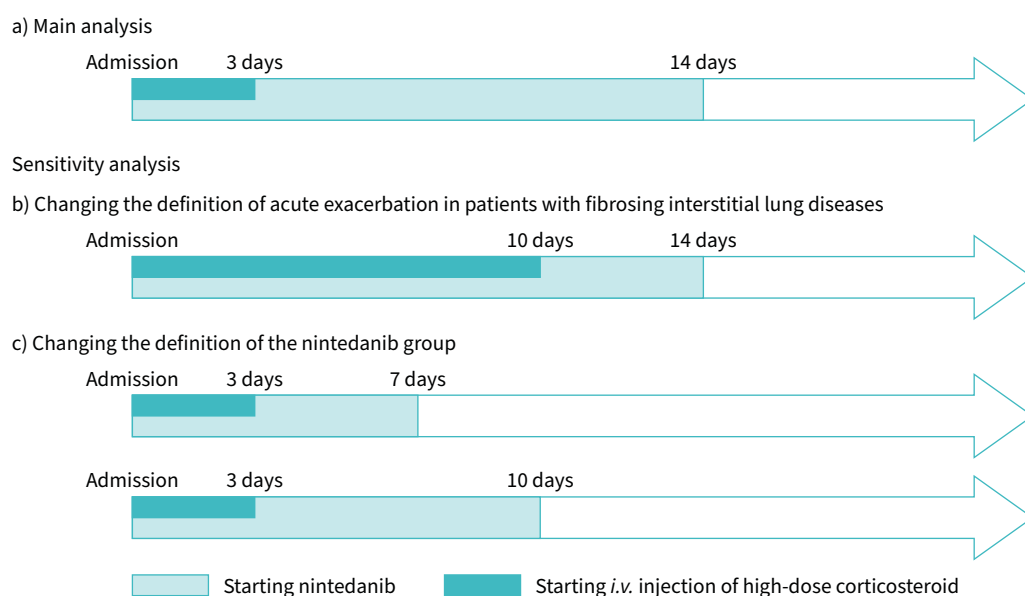FIGURE 1 Graphical summary of the main and sensitivity analyses. a) Initiation periods of nintedanib and *i.v.* high-dose corticosteroid therapy in the main analysis. b) Change from 3 days to 10 days after admission of *i.v.* injection of high-dose corticosteroid for the definition of acute exacerbation. c) Change from 14 days to 7 days or 10 days after admission for the definition of the nintedanib group.

"nintedanib group" (*i.e.* the prescription of nintedanib within 7 days and 10 days after admission, instead of the 14 days in the main analysis). Thus, we examined the therapeutic effect of nintedanib using four combinations of the definition of acute exacerbation in fibrosing ILDs and the nintedanib group.

For the fourth sensitivity analysis, we excluded patients with sepsis, acute respiratory distress syndrome and pneumonias which are specifically diagnosed, treated and usually severe (*e.g.* pneumocystis pneumonia, *Legionella* pneumonia, cytomegalovirus pneumonia, *Pseudomonas aeruginosa* pneumonia and methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia) at admission before calculating propensity scores. In real-world practice, distinguishing these diseases from acute exacerbation of fibrosing ILDs could be challenging. A graphical summary of the sensitivity analyses is shown in figure 1.

## Results
### Patient characteristics
We identified 6235 eligible patients with fibrosing ILDs who required high-dose corticosteroid therapy within 3 days after hospitalisation. Among these, 353 patients newly received nintedanib within 14 days after hospitalisation (the nintedanib group); the other 5882 patients were defined as the control group. A flow diagram of the study is shown in figure 2.

The baseline characteristics of the eligible patients are shown in table 1. More patients in the nintedanib group than in the control group were aged $\geqslant75$ years, obese (BMI $\geqslant30.0$ kg·m$^{-2}$), heavy smokers (pack-years: 41–60 and $\geqslant61$), had received pirfenidone, and were admitted between April 2018 and March 2019. The control group had higher proportions of individuals aged 65–74 years, with Charlson Comorbidity Index $\geqslant2$, smoking history of never and $\leqslant20$ pack-years, Hugh-Jones dyspnoea scale score of 4, fully independent and independent status in activities of daily living, admission between April 2016 and March 2017, and mean number of admissions at the index hospitalisation. These imbalances in baseline characteristics between the two groups were corrected after the overlap propensity score weighting. The C-statistic in the propensity score model was 0.89.

Comorbidities on admission and the treatment of eligible patients are shown in table 2. More patients in the nintedanib group than in the control group had IPF, bacterial pneumonia, COPD, heart disease and



36 395 patients with fibrosing ILDs enrolled in the DPC database from September 2015 to March 2020
    1) First hospitalisation requiring *i.v.* injection of high-dose corticosteroid therapy
    2) No previous prescription of nintedanib
    3) Confirmed hospital visit within 90 days prior to the index hospitalisation

28 277 patients ineligible for this study
    1) Receipt of *i.v.* injection of high-dose corticosteroid after 4 days of admission
    2) No prescription of oral corticosteroid within 14 days after admission
    3) Prescription of pirfenidone during the hospitalisation

8118 patients eligible for this study

1883 patients excluded for immortal time bias
    1) In-hospital death or discharge within 14 days after admission
    2) Receipt of mechanical ventilation with tracheal intubation within 14 days after admission

6235 patients enrolled in the analysis

Initiation of nintedanib within 14 days after admission

Yes → Nintedanib group: 353 patients
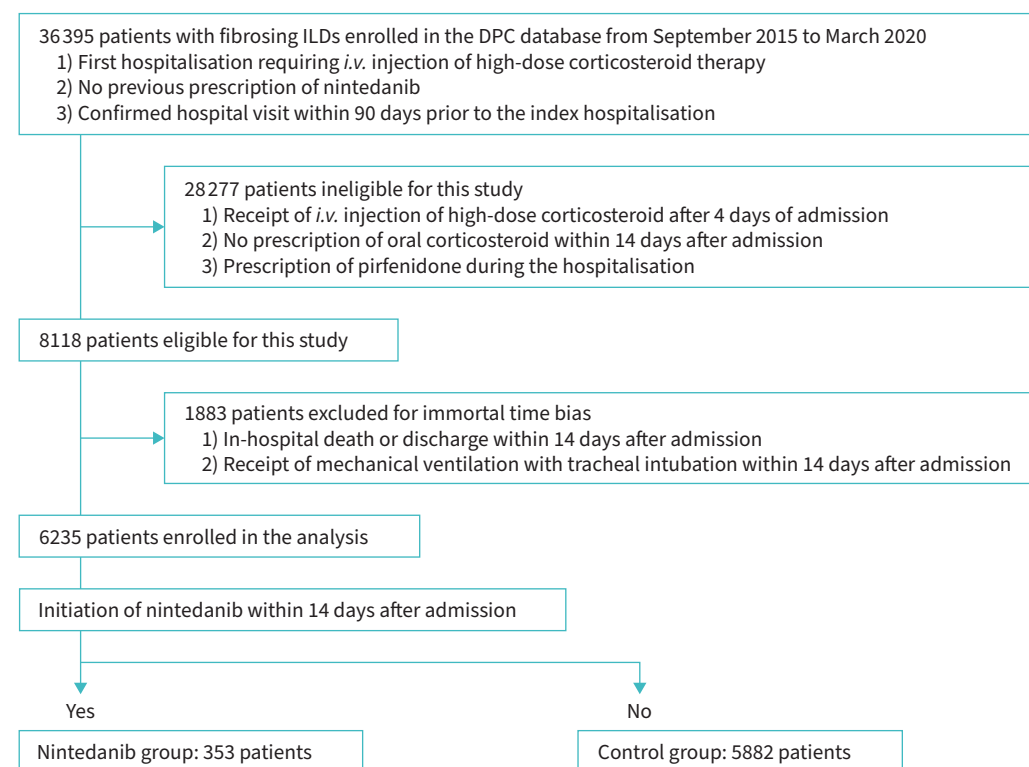
No → Control group: 5882 patients

FIGURE 2 Flow diagram of the study. ILD: interstitial lung disease; DPC: Diagnosis Procedure Combination.

TABLE 1 Baseline characteristics of eligible patients in the original and adjusted cohorts

| | Original cohort | | | Adjusted cohort | | |
|---|---|---|---|---|---|---|
| | Control group (n=5882) | Nintedanib group (n=353) | SMD | Control group (n=3118) | Nintedanib group (n=3118) | SMD |
| Male | 4149 (70.5) | 258 (73.1) | 0.06 | 2382 (76.4) | 2382 (76.4) | 0.00 |
| **Age (years)** | | | | | | |
| <65 | 1013 (17.2) | 53 (15.0) | −0.06 | 577 (18.5) | 577 (18.5) | 0.00 |
| 65–74 | 2192 (37.3) | 90 (25.5) | −0.26 | 870 (27.9) | 870 (27.9) | 0.00 |
| ⩾75 | 2677 (45.5) | 210 (59.5) | 0.28 | 1670 (53.6) | 1670 (53.6) | 0.00 |
| **BMI (kg·m⁻²)** | | | | | | |
| <18.5 | 665 (11.3) | 46 (13.0) | 0.05 | 353 (11.3) | 353 (11.3) | 0.00 |
| 18.5–24.9 | 3415 (58.1) | 206 (58.4) | 0.06 | 1762 (56.5) | 1762 (56.5) | 0.00 |
| 25.0–29.9 | 1388 (23.6) | 75 (21.3) | −0.06 | 697 (22.4) | 697 (22.4) | 0.00 |
| ⩾30.0 | 127 (2.2) | 19 (5.4) | 0.17 | 219 (7.0) | 219 (7.0) | 0.00 |
| Missing | 287 (4.9) | 7 (2.0) | −0.16 | 87 (2.8) | 87 (2.8) | 0.00 |
| **CCI** | | | | | | |
| 0–1 | 2500 (42.5) | 140 (39.7) | −0.06 | 1311 (42.0) | 1311 (42.0) | 0.00 |
| ⩾2 | 2051 (34.9) | 96 (27.2) | −0.17 | 869 (27.9) | 869 (27.9) | 0.00 |
| Missing | 1331 (22.6) | 117 (33.1) | 0.24 | 937 (30.1) | 937 (30.1) | 0.00 |
| **Smoking history (pack-years)** | | | | | | |
| Never | 2471 (42.0) | 77 (21.8) | −0.44 | 718 (23.0) | 718 (23.0) | 0.00 |
| ⩽20 | 628 (10.7) | 21 (5.9) | −0.17 | 244 (7.8) | 244 (7.8) | 0.00 |
| 21–40 | 1090 (18.5) | 63 (17.8) | −0.02 | 608 (19.5) | 608 (19.5) | 0.00 |
| 41–60 | 615 (10.5) | 50 (14.2) | 0.11 | 411 (13.2) | 411 (13.2) | 0.00 |
| ⩾61 | 534 (9.1) | 101 (28.6) | 0.52 | 842 (27.0) | 842 (27.0) | 0.00 |
| Missing | 544 (9.2) | 41 (11.6) | 0.08 | 295 (9.5) | 295 (9.5) | 0.00 |
| **Hugh-Jones dyspnoea scale** | | | | | | |
| 1 | 540 (9.2) | 36 (10.2) | 0.03 | 392 (12.6) | 392 (12.6) | 0.00 |
| 2 | 655 (11.1) | 40 (11.3) | 0.01 | 335 (10.8) | 335 (10.8) | 0.00 |
| 3 | 864 (14.7) | 55 (15.6) | 0.03 | 515 (16.5) | 515 (16.5) | 0.00 |
| 4 | 1279 (21.7) | 52 (14.7) | −0.18 | 544 (17.4) | 544 (17.4) | 0.00 |
| 5 | 1489 (25.3) | 101 (28.6) | 0.07 | 868 (27.9) | 868 (27.9) | 0.00 |
| Missing | 1055 (17.9) | 69 (19.5) | 0.04 | 463 (14.9) | 463 (14.9) | 0.00 |
| **ADL score (Barthel index)** | | | | | | |
| Fully independent | 2653 (45.1) | 124 (35.1) | −0.21 | 1133 (36.3) | 1133 (36.3) | 0.00 |
| Independent | 827 (14.1) | 20 (5.7) | −0.28 | 242 (7.8) | 242 (7.8) | 0.00 |
| Dependent | 1546 (26.3) | 91 (25.8) | −0.01 | 782 (25.1) | 782 (25.1) | 0.00 |
| Missing | 856 (14.6) | 118 (33.4) | 0.45 | 960 (30.8) | 960 (30.8) | 0.00 |
| **Preceding pirfenidone** | 389 (6.6) | 38 (10.8) | 0.15 | 311 (10.0) | 310 (10.0) | 0.00 |
| **Preceding OCS** | 948 (16.1) | 32 (9.1) | −0.21 | 356 (11.4) | 356 (11.4) | 0.00 |
| **Admission year** | | | | | | |
| September 2015–March 2016 | 650 (11.1) | 35 (9.9) | −0.04 | 283 (9.1) | 283 (9.1) | 0.00 |
| April 2016–March 2017 | 964 (16.4) | 29 (8.2) | −0.25 | 288 (9.2) | 288 (9.2) | 0.00 |
| April 2017–March 2018 | 1288 (21.9) | 89 (25.2) | 0.08 | 817 (26.2) | 817 (26.2) | 0.00 |
| April 2018–March 2019 | 1701 (28.9) | 120 (34.0) | 0.11 | 1044 (33.5) | 1044 (33.5) | 0.00 |
| April 2019–March 2020 | 1279 (21.7) | 80 (22.7) | 0.02 | 686 (22.0) | 686 (22.0) | 0.00 |
| **Admissions (n)** | 11.2±16.9 | 8.6±6.4 | −0.20 | 8.5±10.7 | 8.5±6.2 | 0.00 |

Data are presented as n (%) or mean±SD, unless otherwise stated. SMD: standardised mean difference; BMI: body mass index; CCI: Charlson Comorbidity Index; ADL: activities of daily living; OCS: oral corticosteroid.

GORD. More patients in the control group than in the nintedanib group had liver disease, cancer, diabetes mellitus, osteoporosis and thyroid diseases. The mean number of days from admission to *i.v.* injection of high-dose corticosteroid was higher in the control group. These imbalances in comorbidities on admission and during treatment between the two groups were corrected after the overlap propensity score weighting.

## Outcomes

In-hospital death and length of hospital stay are shown in table 3. In the original cohort, in-hospital mortality was lower in the nintedanib group (6.0%) than in the control group (13.7%; p<0.001). The mean±SD length of hospital stay in patients who were discharged alive was shorter in the nintedanib group (30.4±12.6 days) than in the control group (39.9±22.2 days; p<0.001). After adjusting the cohort using

**TABLE 2** Comorbidities and treatment of eligible patients in the original and adjusted cohorts

| | Original cohort | | | Adjusted cohort | | |
|---|---|---|---|---|---|---|
| | Control group (n=5882) | Nintedanib group (n=353) | SMD | Control group (n=3118) | Nintedanib group (n=3118) | SMD |
| **Comorbidities** | | | | | | |
| IPF | 1941 (33.0) | 277 (78.5) | 1.03 | 2207 (70.8) | 2207 (70.8) | 0.00 |
| Respiratory failure | 2255 (38.3) | 139 (39.4) | 0.02 | 1240 (39.8) | 1240 (39.8) | 0.00 |
| Bacterial pneumonia | 618 (10.5) | 59 (16.7) | 0.18 | 463 (14.8) | 463 (14.8) | 0.00 |
| COPD | 876 (14.9) | 77 (21.8) | 0.18 | 622 (20.0) | 622 (20.0) | 0.00 |
| Pneumothorax | 50 (0.9) | 2 (0.6) | −0.03 | 26 (0.8) | 26 (0.8) | 0.00 |
| Heart disease | 826 (14.0) | 64 (18.1) | 0.11 | 468 (15.0) | 468 (15.0) | 0.00 |
| Liver disease | 321 (5.5) | 9 (2.6) | −0.15 | 115 (3.7) | 115 (3.7) | 0.00 |
| GORD | 1264 (21.5) | 107 (30.3) | 0.20 | 900 (28.9) | 900 (28.9) | 0.00 |
| Cancer | 896 (15.2) | 36 (10.2) | −0.15 | 388 (12.4) | 388 (12.4) | 0.00 |
| Bronchial asthma | 344 (5.9) | 20 (5.7) | −0.01 | 255 (8.2) | 255 (8.2) | 0.00 |
| Hypertension | 1389 (23.6) | 74 (21.0) | −0.06 | 647 (20.8) | 647 (20.8) | 0.00 |
| Diabetes mellitus | 2199 (37.4) | 86 (24.4) | −0.29 | 885 (28.4) | 885 (28.4) | 0.00 |
| Osteoporosis | 834 (14.2) | 21 (6.0) | −0.28 | 244 (7.8) | 244 (7.8) | 0.00 |
| Thyroid diseases | 151 (2.6) | 4 (1.1) | −0.11 | 50 (1.6) | 50 (1.6) | 0.00 |
| **Treatment** | | | | | | |
| Time from admission to high-dose *i.v.* corticosteroid therapy (days) | 1.41±0.67 | 1.25±0.62 | −0.25 | 1.29±0.56 | 1.29±0.65 | 0.00 |
| NPPV within 14 days | 871 (14.8) | 56 (15.9) | 0.03 | 479 (15.4) | 479 (15.4) | 0.00 |

Data are presented as n (%) or mean±SD, unless otherwise stated. SMD: standardised mean difference; IPF: idiopathic pulmonary fibrosis; GORD: gastro-oesophageal reflux disease; NPPV: noninvasive positive pressure ventilation.

overlap propensity score weighting, in-hospital mortality was lower in the nintedanib group (7.1%) than in the control group (15.1%; p<0.001). The mean±SD length of hospital stay in patients who were discharged alive was shorter in the nintedanib group (30.7±13.7 days) than in the control group (37.5±19.0 days; p<0.001). Logistic regression analyses in the adjusted cohort showed that the odds ratio of in-hospital death in the nintedanib group was 0.43 (95% CI 0.27–0.70; p=0.001).

For subgroup analysis, the adjusted cohort was divided into IPF patients or non-IPF patients. In patients with IPF, the in-hospital mortality was lower in the nintedanib group (8.9%) than in the control group (14.0%; p<0.001). Logistic regression analyses showed that the odds ratio of in-hospital death in the nintedanib group was 0.60 (95% CI 0.35–1.03; p=0.062). In non-IPF patients, the in-hospital mortality was also lower in the nintedanib group (2.8%) than in the control group (17.7%; p<0.001). Logistic regression analyses showed that the odds ratio of in-hospital death in the nintedanib group was 0.13 (95% CI 0.03–0.56; p=0.006).

In-hospital deaths of the three sensitivity analyses based on the different definitions of acute exacerbation in fibrosing ILDs and the nintedanib group are shown in table 4. First, we changed the definition of acute

**TABLE 3** Outcomes with or without nintedanib in the original and adjusted cohorts

| | Original cohort | | | Adjusted cohort | | |
|---|---|---|---|---|---|---|
| | Control group (n=5882) | Nintedanib group (n=353) | p-value | Control group (n=3118) | Nintedanib group (n=3118) | p-value |
| **In-hospital death** | 804 (13.7) | 21 (6.0) | <0.001 | 471 (15.1) | 222 (7.1) | <0.001 |
| **Length of hospital stay (days)** | 39.9±22.2 | 30.4±12.6 | <0.001 | 37.5±19.0 | 30.7±13.7 | <0.001 |

Data are presented as n (%) or mean±SD, unless otherwise stated. After overlap propensity score weighting, nintedanib treatment was significantly associated with lower in-hospital mortality in the adjusted cohort (OR 0.43, 95% CI 0.27–0.70; p=0.001).

**TABLE 4** Sensitivity analyses for in-hospital death in the adjusted cohorts

| High-dose corticosteroid | Nintedanib initiation | Patients in each group (n) | OR (95% CI) | p-value |
|---|---|---|---|---|
| **Within 10 days** | Within 14 days | 4000 | 0.67 (0.45–0.97) | 0.036 |
| **Within 3 days** | Within 7 days | 2262 | 0.63 (0.34–1.19) | 0.157 |
| | Within 10 days | 2476 | 0.40 (0.22–0.73) | 0.003 |

exacerbation by altering the period of *i.v.* injection of high-dose corticosteroid from 3 days after admission (in the main analysis) to 10 days. The odds ratio of in-hospital death in the nintedanib group was 0.67 (95% CI 0.45–0.97; p=0.036), after the overlap propensity score weighting (n=4000 patients in each group). Next, we changed the period used for the definition of the nintedanib group from 14 days to 7 days (n=2262 patients) or 10 days (n=2476 patients) after admission. After overlap propensity score weighting, the odds ratios of in-hospital death in the nintedanib group were 0.63 (95% CI 0.34–1.19; p=0.157) and 0.40 (95% CI 0.22–0.73; p=0.003) for 7 and 10 days after admission, respectively.

In the fourth sensitivity analysis, we found and excluded patients with sepsis (n=51 patients), acute respiratory distress syndrome (n=44 patients), pneumocystis pneumonia (n=95 patients), *Legionella* pneumonia (n=3 patients), cytomegalovirus pneumonia (n=69 patients), *P. aeruginosa* pneumonia (n=2 patients) and MRSA pneumonia (n=0 patients) at admission using ICD-10 codes. After excluding these patients, we recalculated the propensity scores for receiving nintedanib treatment and performed overlap propensity score weighting. In this adjusted cohort, the in-hospital mortality was lower in the nintedanib group (7.2%) than in the control group (14.8%; p<0.001). Logistic regression analyses in the adjusted cohort showed that the odds ratio of in-hospital death in the nintedanib group was 0.45 (95% CI 0.28–0.73; p=0.001).

## Discussion

This study showed that in an overlap propensity score weighting-adjusted cohort, the use of nintedanib within 14 days after admission was significantly associated with a lower risk of in-hospital death and a shorter length of hospital stay in patients with fibrosing ILDs who received *i.v.* injection of high-dose corticosteroid. To the best of our knowledge, this study provides the first evidence regarding the therapeutic effect of nintedanib during the treatment of acute exacerbation in patients with fibrosing ILDs in a nationwide clinical setting.

Poor outcomes of acute exacerbation of IPF and fibrosing ILDs are an urgent clinical problem [16]. Although no randomised controlled trials on corticosteroid treatment in acute exacerbation of fibrosing ILDs are available, high-dose corticosteroids are recommended in the management guidelines of acute exacerbation of IPF [1, 5] and a review of acute exacerbation of fibrosing ILDs [17], and are frequently used in the real-world to treat acute exacerbation of fibrosing ILDs. However, the evidence of the treatment of acute exacerbations of IPF and fibrosing ILDs has not been well established. Until now, the benefits of corticosteroid [6], cyclophosphamide [18] and thrombomodulin alfa [19] have not been evident in patients with acute exacerbations of IPF. Although nintedanib reportedly reduced the risk of acute exacerbations of IPF [20] and fibrosing ILDs [3], the role of nintedanib during acute exacerbation in patients with ILDs has not been studied. Our study is consistent with a previous study which utilised propensity score matching analyses and showed that the use of antifibrotic treatment, such as nintedanib and pirfenidone therapies, before the onset of acute exacerbation was associated with a lower rate of mortality attributed to acute exacerbation in patients with IPF [21]. However, our study is different from the aforementioned study for the following reasons: 1) patients with fibrosing ILDs other than IPF were included in the present study, 2) all patients in the current study were most likely first-time users of high-dose corticosteroid therapy, 3) nintedanib was prescribed only after hospitalisation for acute exacerbation in our cohort and 4) nintedanib was prescribed during acute exacerbation treatment in our patients. In this way, our study showed for the first time that the use of nintedanib during acute exacerbation was significantly associated with a lower mortality rate in patients with fibrosing ILDs, including IPF.

To confirm the robustness of the main results, we conducted several sensitivity analyses using different definitions for acute exacerbation in patients with fibrosing ILDs and for the nintedanib group (*i.e.* the date of *i.v.* injection of high-dose corticosteroid and the date of prescription of nintedanib). Acute exacerbation may exhibit a variable clinical course: some patients may have presented with severe respiratory failure at admission and were treated immediately with an *i.v.* injection of high-dose corticosteroid, while others may have presented with relatively mild respiratory failure at admission but subsequently experienced

deteriorated respiratory conditions during hospitalisation. Patients who required *i.v.* injection of high-dose corticosteroid within 3 days may have mostly included the former group of patients, whereas patients who required *i.v.* injection of high-dose corticosteroid within 10 days after admission may have mostly included the latter group. Because the results were similar in both settings, nintedanib therapy may be beneficial in patients with acute exacerbation regardless of their clinical course. Moreover, in our sensitivity analyses, we evaluated two earlier time-points of starting nintedanib (*i.e.* 7 and 10 days after admission) in addition to the 14 days after admission in the main analysis. Nintedanib reduced the risk of in-hospital death in patients with acute exacerbation of fibrosing ILDs when it was started within all three time-points. Therefore, nintedanib may be effective when it is started as soon as the patient is capable of receiving oral medication.

Other clinical questions include whether there is a difference in the mortality of acute exacerbation and the efficacy of nintedanib between IPF and non-IPF patients. In our adjusted cohort, there was no difference in the mortality of acute exacerbation between patients with IPF and non-IPF. The use of nintedanib was associated with a lower risk of in-hospital death in patients restricted to the IPF or non-IPF groups.

In real-world practice, sepsis, acute respiratory distress syndrome and pneumonias, such as pneumocystis pneumonia, *Legionella* pneumonia, cytomegalovirus pneumonia, *P. aeruginosa* pneumonia and MRSA pneumonia, at admission are usually severe, and distinguishing these from acute exacerbation of fibrosing ILDs could be challenging. In the adjusted cohort that excluded these patients, the use of nintedanib was significantly associated with a lower risk of in-hospital death.

This study had some limitations. First, the Diagnosis Procedure Combination database does not contain imaging examination findings (*e.g.* chest radiography and chest computed tomography) or patients' respiratory status. In this study, *i.v.* injection of high-dose corticosteroid was used as a proxy for acute exacerbation onset. Our definition of acute exacerbation in patients with fibrotic ILDs may not fully capture the onset of acute exacerbation in patients with fibrotic ILDs, especially in those with mild acute exacerbation who did not receive *i.v.* injection of high-dose corticosteroid. Second, the results of this study may not be applicable to patients who died, were discharged or received mechanical ventilation with tracheal intubation 7 days after admission. These patients were excluded to account for immortal time bias in our sensitivity analyses, which used the prescription of nintedanib within 7 days after admission for the definition of the nintedanib group.

In conclusion, this study showed that the use of nintedanib during the treatment of acute exacerbation was significantly associated with a lower risk of in-hospital death and a shorter length of hospital stay in patients with fibrosing ILDs, after adjustments using overlap propensity score weighting. Our results elucidate the potential role of nintedanib in the treatment of acute exacerbation in patients with fibrosing ILDs. Further prospective studies are required.

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