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## Efficacy and safety of nintedanib for pulmonary fibrosis in severe pneumonia induced by COVID-19: An interventional study



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### ARTICLE INFO

#### Article history:

Received 12 April 2021

Received in revised form 17 May 2021

Accepted 21 May 2021

#### Keywords:

COVID-19

Respiratory distress syndrome

Pulmonary fibrosis

Nintedanib

Respiration

Artificial

Intensive care units

### ABSTRACT

**Objectives:** One of the most significant features of poor prognosis in COVID-19 is pulmonary fibrosis. Nintedanib is a new antifibrotic agent that interferes with processes of pulmonary fibrosis. This study aimed to investigate the efficacy and safety of nintedanib in COVID-19.

**Methods:** This was an interventional study in which adult patients with COVID-19 requiring mechanical ventilation were consecutively enrolled. The primary endpoint was 28-day mortality after the initiation of mechanical ventilation. The secondary endpoints were length of mechanical ventilation, volume of lung injury, and the incidence of gastrointestinal adverse events and acute liver failure.

**Results:** Thirty patients with COVID-19 underwent nintedanib therapy. We included 30 patients not receiving nintedanib as the historical control group. There were no significant differences in 28-day mortality between the groups (23.3% vs 20%,  $P=0.834$ ). Lengths of mechanical ventilation were significantly shorter in the nintedanib group ( $P=0.046$ ). Computed tomography volumetry showed that the percentages of high-attenuation areas were significantly lower in the nintedanib group at liberation from mechanical ventilation (38.7% vs 25.7%,  $P=0.027$ ). There were no significant differences in the adverse events.

**Conclusions:** The administration of nintedanib may offer potential benefits for minimizing lung injury in COVID-19.

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### Introduction

SARS-CoV-2, a novel RNA coronavirus, was identified in early January 2020 as the cause of a severe pneumonia in Wuhan, China. After causing the deaths of thousands of patients in China, SARS-CoV-2 infection (COVID-19) has rapidly spread worldwide (Zhu et al., 2020). As of February 15, 2021, more than 108.0 million confirmed infections, with approximately 2.4 million deaths, were

reported from 223 countries and territories around the world (WHO Coronavirus Disease Dashboard, 2021).

COVID-19 mainly affects the respiratory system, with some patients rapidly progressing to severe acute respiratory distress syndrome (ARDS), which has appeared to be associated with increased risk of death (Burki, 2020). The mortality rate among patients with COVID-19-induced ARDS requiring mechanical ventilation has actually ranged widely between 35.7% to 94% and is considerably higher than that of COVID-19 patients without ARDS (Auld et al., 2020; Wu et al., 2020; Sinha et al., 2020). One of the most significant features of poor prognosis in COVID-19-induced ARDS is the development of pulmonary fibrosis. Pulmonary fibrosis is a pathological consequence of interstitial lung diseases that is characterized by unsuccessful reconstruction of the damaged alveolar epithelium, persistence of fibroblasts and excessive deposition of collagen (Sime and O'Reilly, 2001). Histopathologically, 3 phases are recognized during the evolution

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of lung injury in ARDS: exudative, proliferative, and fibrotic. In the proliferative phase, type II alveolar cells proliferate with epithelial cell regeneration and remodeling, together with proliferation of fibroblasts. Subsequently, the third fibrotic phase involving collagen deposition in alveolar, vascular, and interstitial beds progresses in some patients, leading to irreversible development of cystic changes and limited functional recovery (Tomashefski Jr, 2000). A number of clinical, radiological and histopathological studies have suggested that the progression of pulmonary fibrosis commonly complicating severe COVID-19 patients can potentially worsen survival and functional outcomes (Pan et al., 2020; Schwensen et al., 2020; Tian et al., 2020; Zhou et al., 2020). In this context, several antifibrotic agents are expected to be beneficial treatments to prevent the progression of pulmonary fibrosis in severe COVID-19-induced ARDS.

Nintedanib is an intracellular inhibitor of tyrosine kinases that is reported in several preclinical studies to interfere with processes of active fibrosis such as proliferation, migration and differentiation of fibroblasts (Wollin et al., 2014, 2015; Redente et al., 2018). Recently, several large clinical trials showed that treatment with nintedanib reduced the rate of decline in forced vital capacity in patients with idiopathic pulmonary fibrosis (IPF) and systemic sclerosis-associated interstitial lung disease (Richeldi et al., 2011, 2014; Distler et al., 2019).

Herein, we hypothesized that treatment with nintedanib could improve the survival and functional outcomes in severe COVID-19-induced ARDS by inhibiting the progression of pulmonary fibrosis, and we conducted an interventional study using a historical control to investigate the efficacy and safety of nintedanib in patients with COVID-19-induced ARDS.

## Methods

### Study design and setting

We undertook a single-center interventional study using a historical control conducted in the intensive care unit (ICU) of a tertiary care hospital in Japan. A data monitoring committee provided independent assessment of the safety, scientific validity and integrity of the trial. Also, an independent investigator who was unaware of the group assignments reviewed medical documentation to adjudicate the primary cause of all deaths and all adverse events. This trial was conducted in accordance with the principles of the Declaration of Helsinki and the Japanese Clinical Trials Act (Act No. 16 of April 14, 2017).

The use of nintedanib (OFEV®) for patients with COVID-19 is not yet approved by the Japanese Ministry of Health, Labor and Welfare. The trial protocol was approved by the Institutional Review Board for Clinical Research of Osaka General Medical Center as a specified clinical trial (IRB No. S202004004) and is available at the Japanese Registry of Clinical Trials (jRCTs051200036). Before study inclusion, written informed consent was obtained from all patients who received nintedanib.

### Participants

Patients admitted to the ICU with the diagnosis of COVID-19 were consecutively recruited from August to October 2020 and were eligible for the nintedanib group if they were 20 years of age or older and required mechanical ventilation.

The exclusion criteria included a history of IPF or chronic liver failure (Child Pugh B or C), breastfeeding, pregnancy, a history or proven risk factors of thrombosis, proven risk factors of bleeding, unavailable to use an enteral tube, limitation of sustained life care, and post-cardiopulmonary arrest resuscitation status at the time of diagnosis of COVID-19. As the historical control group, we

consecutively enrolled from March to July 2020 an equal number of the most recent consecutive adult patients with COVID-19 who required mechanical ventilation and did not meet the exclusion criteria.

### Sample size

Because there were no previous data on the survival benefit of nintedanib for patients with COVID-19, we could not calculate a sample size. However, previous studies suggested that 15 to 30 participants per group are required to ensure statistical validity of the results in a pilot study (Hertzog, 2008; Viechtbauer et al., 2015). Therefore, we decided to include a total of 60 participants with 30 participants per group.

### Diagnosis of COVID-19

The diagnosis of COVID-19 was performed according to World Health Organization interim guidance (World Health Organization, 2021) and confirmed by RNA detection of the SARS-CoV-2 in a clinical laboratory of the Osaka Institute of Public Health. We defined the first day of mechanical ventilation as “day 1” both in the nintedanib and control groups.

### Treatment

Nintedanib therapy consisted of 150 mg of nintedanib administered via nasogastric tube twice daily from day 1 to liberation from mechanical ventilation within 28 days. We also used favipiravir, a new antiviral agent, for both the nintedanib and historical control groups unless contraindications were present. Mechanical ventilation for all study patients was typically conducted according to The National Institutes of Health treatment guidelines for COVID-19-related ARDS (The National Institutes of Health, 2021). Other supportive care during mechanical ventilation was given per institutional policies and the discretion of the treating physicians.

### Data collection and outcomes

Patients were followed up until hospital discharge or death. Patient information collected included demographic characteristics, pre-existing comorbidities (assessed by Charlson comorbidity index), laboratory tests, severity scores and therapeutic interventions. Severity of illness was evaluated according to the PaO<sub>2</sub>/FiO<sub>2</sub> (P/F) ratio, the Sequential Organ Failure Assessment (SOFA) score, and the Acute Physiology and Chronic Health Evaluation (APACHE) II score. The APACHE II and SOFA scores were evaluated at day 1, and the P/F ratio was evaluated every day during mechanical ventilation. The primary endpoint was 28-day mortality after the initiation of mechanical ventilation. The secondary endpoints were 1) length of mechanical ventilation, 2) time-related alteration in the P/F ratio over 14 days during mechanical ventilation, 3) computed tomographic (CT) quantitative evaluation for lung injury in surviving patients, and 4) the incidence of gastrointestinal adverse events and acute liver failure within 28 days after the initiation of mechanical ventilation. The length of mechanical ventilation was evaluated by Kaplan-Meier methods and the number of ventilator-free days within 28 days.

Quantitative CT volumetry of the high-attenuation areas, including both ground-glass opacities and consolidation, was conducted at the time of initiation of and liberation from mechanical ventilation (Supplementary Figure S1). The segmentation of the high-attenuation areas was conducted by 2 physicians blinded from the patient data and treatment allocation (K.M. and Y.M.). Volumes of high-attenuation areas were calculated by another

investigator blinded from the patient data and treatment allocation (N.O.) using a digital image analysis application (fcuro-label, fcuro Co., Ltd., Osaka, Japan).

Gastrointestinal adverse complications were defined as the following 3 events: 1) mild events including occurrence of vomiting and diarrhea (more than 4 times per day), 2) moderate events including mild to moderate gastrointestinal bleeding or total parenteral nutrition requirements, and 3) severe events requiring surgical or endoscopic intervention (e.g., intestinal perforation and massive gastrointestinal bleeding). The incidence of acute liver failure was defined as the elevation in serum aspartate aminotransferase or alanine aminotransferase to levels of 1.5 (mild event), 5 (moderate event), or 10 times (severe event) above the upper limit of normal range.

### Statistical analysis

Descriptive statistics are calculated as medians (interquartile range) or proportions (numbers), as appropriate. Univariate differences between groups were assessed using the Mann-Whitney U test or chi-square test, as appropriate. Missing values were not imputed in any of the regression models. To assess the time-related alteration in the P/F ratio, we fitted a multilevel mixed-effects regression model with fixed effects assigned to patient categorization (the control or the nintedanib groups), time points during mechanical ventilation and two-way interaction term for these independent variables, and random effects assigned to individual identification numbers. Kaplan–Meier curves were constructed to evaluate 28-day mortality and length of mechanical ventilation. A log-rank test was conducted for 28-day mortality, and the Gehan–Breslow–Wilcoxon test was conducted for the length of mechanical ventilation to compare the Kaplan–Meier curves between 2 groups. All statistical inferences were performed with a two-sided P at the 5% significance level. Because of the underpowered nature of the interaction analysis, we used a two-sided significance level of 20% with statistical inferences for the interaction analyses (Ramos et al., 2008). All statistical analyses were conducted using STATA Data Analysis and Statistical Software version 15.0 (StataCorp, College Station, TX).

## Results

### Study population

The patient flow diagram is shown in Figure 1. From August to October 2020, 33 consecutive patients were admitted to the ICUs with the diagnosis of COVID-19 and underwent mechanical

ventilation. After excluding 3 patients who met the exclusion criteria, 30 patients were enrolled in this study and underwent the nintedanib therapy (nintedanib group). We also included the 30 most recent consecutive adult patients with COVID-19 who required mechanical ventilation and did not meet the exclusion criteria from March to July 2020 as the control group.

Baseline characteristics, laboratory tests and illness severity scores obtained on day 1 in the 2 groups are shown in Table 1. Age, sex and body mass index were similar between the 2 groups. Although the nintedanib group had a significantly higher rate of chronic respiratory disease, rates of other preexisting comorbidities were not significantly different, and the Charlson comorbidity index was similar between the groups. Similarly, there were no significant differences between the groups in physiological and laboratory parameters on day 1, including Glasgow Coma Scale score, body temperature, P/F ratio, white blood cell and platelet counts, and C-reactive protein, creatinine and total bilirubin levels.

There was no significant difference between the 2 groups in therapeutic interventions, such as the use of corticosteroids, favipiravir, veno-venous extracorporeal membrane oxygenation, prone position and low-dose unfractionated heparin for prophylaxis against venous thromboembolism.

### Effect of treatment on survival and lung injury

The survival curves and lengths of mechanical ventilation are shown in Figure 2. The 28-day mortality rate was 23.3% (7 of 30 patients) in the control group versus 20% (6 of 30 patients) in the nintedanib group. The difference between the 2 groups was not significant ( $P=0.834$ , log-rank test). However, the lengths of mechanical ventilation were significantly shorter in the nintedanib group ( $P=0.046$ , Gehan–Breslow–Wilcoxon test). Furthermore, the median number of ventilator-free days within 28 days was significantly longer in the nintedanib group (12 vs 17 days,  $P=0.038$ , Table 2).

A multilevel mixed-effects regression model showed that time-related alterations in P/F ratio within 14 days from the initiation of mechanical ventilation were significantly different between the 2 groups ( $P$  for interaction = 0.005), and the nintedanib group had relatively higher P/F ratios as time advanced compared with those in the control group (Figure 3).

CT volumetry showed that the percentages of high-attenuation areas were not different between the 2 groups at initiation of mechanical ventilation (29.1% vs 30.8%,  $P=0.651$ , Table 2). However, they were significantly lower in the nintedanib group at liberation from mechanical ventilation (38.7% vs 25.7%,  $P=0.027$ , Table 2).

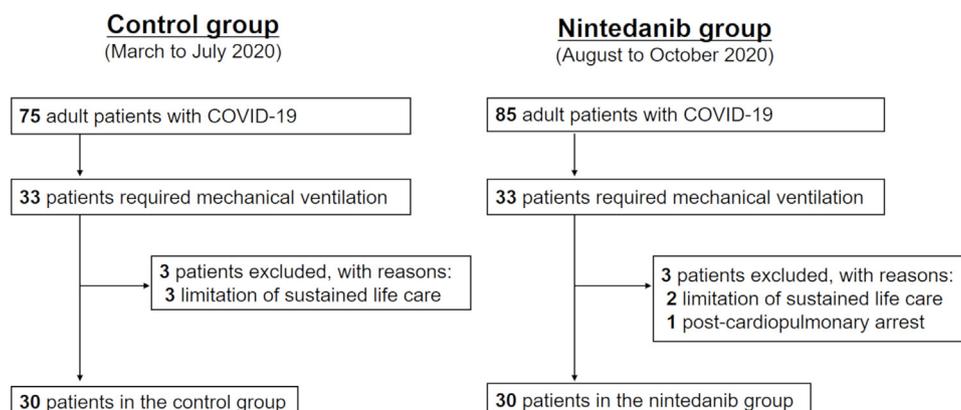
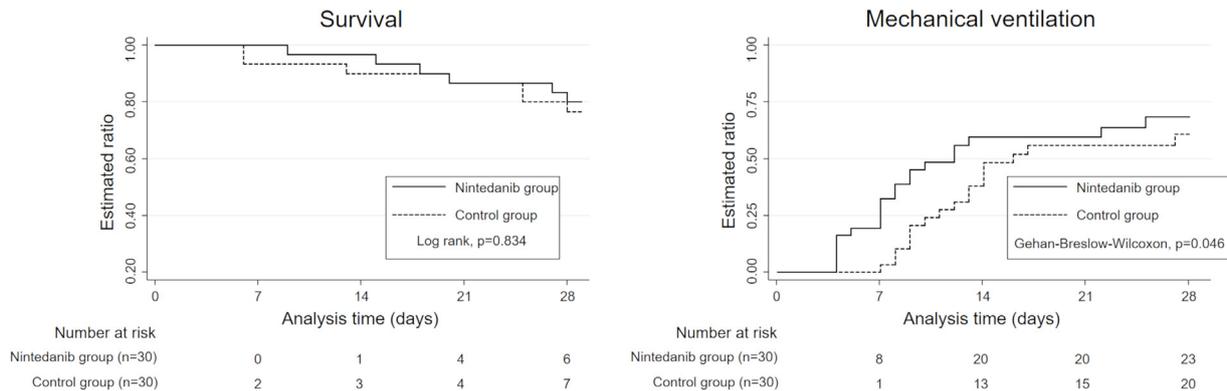


Figure 1. Patient flow diagram. COVID-19 = coronavirus disease 2019.

**Table 1**  
Baseline characteristics, severity and therapeutic interventions.

	Control N = 30	Nintedanib N = 30	P Value
Age, years	70 (62–77)	75 (66–80)	0.109
Sex, male	18 (60%)	23 (76.7%)	0.165
BMI (kg/m <sup>2</sup> )	23.2 (20.9–25.5)	24.6 (20.3–27.9)	0.756
Pre-existing conditions			
Hypertension	16 (53.3%)	19 (63.3%)	0.432
Chronic respiratory disease	4 (13.3%)	12 (40%)	0.020
Chronic heart failure	2 (6.7%)	7 (23.3%)	0.071
Chronic kidney disease	6 (20%)	5 (16.7%)	0.739
Diabetes mellitus	13 (43.3%)	12 (40%)	0.793
Cancer	1 (3.3%)	4 (13.3%)	0.161
Charlson comorbidity index	2 (0–3)	2 (1–4)	0.143
Findings at time of intubation			
Glasgow Coma Scale score	13 (6–15)	11 (3–15)	0.789
Body temperature (°C)	37.4 (36.8–37.7)	37.1 (36.4–37.6)	0.176
PaO <sub>2</sub> /FiO <sub>2</sub> ratio	181 (120–242)	178 (121–255)	0.487
White blood cell count (10 <sup>3</sup> /μL)	7.1 (5.6–9)	7 (3.7–11.9)	0.756
Platelet count (10 <sup>3</sup> /μL)	171 (131–256)	165 (125–209)	0.217
C-reactive protein (mg/dL)	11.8 (7.8–18.2)	10.1 (6.7–15.8)	0.174
Creatinine (mg/dL)	0.9 (0.6–1.1)	0.9 (0.8–1.2)	0.243
Bilirubin (mg/dL)	0.6 (0.5–0.8)	0.6 (0.4–0.9)	0.917
APACHE II score	17 (11–21)	17 (13–24)	0.358
SOFA score	7 (4–8)	7 (5–10)	0.480
ISTH overt-DIC score	0 (0–2)	0 (0–2)	0.963
Therapeutic interventions			
Corticosteroids	26 (86.7%)	29 (96.7%)	0.161
Favipiravir	27 (90%)	23 (76.7%)	0.166
V-V ECMO	4 (13.3%)	3 (10%)	0.688
Prone position	12 (40%)	14 (46.7%)	0.602
Unfractionated heparin	24 (80%)	28 (93.3%)	0.129

BMI, body mass index; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; ISTH, International Society on Thrombosis and Hemostasis; DIC, disseminated intravascular coagulation; V-V ECMO, veno-venous extracorporeal membrane oxygenation.



**Figure 2.** Kaplan–Meier curves for evaluation of 28-day mortality and length of mechanical ventilation. The solid black lines represent patients in the nintedanib group, and the dotted black lines represent patients in the control group. Log rank test was conducted for 28-day mortality, and the Gehan–Breslow–Wilcoxon test was conducted for the length of mechanical ventilation to compare the curves between the groups.

**Adverse events**

The incidence of adverse events in the 2 groups is summarized in Table 2. There were no significant differences in the incidence of mild, moderate and severe gastrointestinal adverse events between the 2 groups. The incidence of mild and moderate acute liver failure was slightly higher in the nintedanib group, but the differences were not statistically significant (P=0.243 and 0.158, respectively). The incidence of severe acute liver failure was not different between the 2 groups.

**Discussion**

As the worldwide deaths from COVID-19 continue to rise, a substantial therapy to suppress lung injury and improve patient

survival is strongly required. In the present study, we investigated the efficacy and safety of nintedanib, a new antifibrotic agent for IPF, in severe COVID-19 patients.

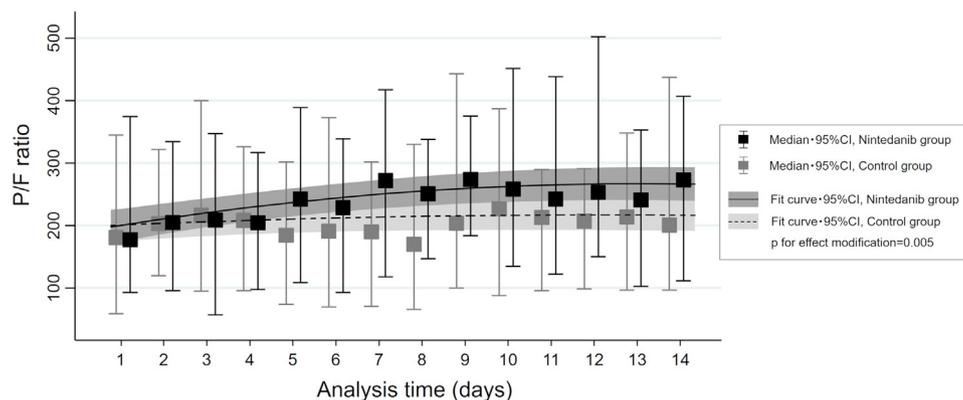
*Effect of nintedanib on lung injury*

Pulmonary fibrosis is a life-threatening pathological consequence of acute and chronic interstitial lung diseases that is characterized by unsuccessful reconstruction of the injured alveolar epithelium, persistence of fibroblasts and excessive deposition of collagen (Sime and O’Reilly, 2001). Recently, a number of studies reported that pulmonary fibrosis was also occurring as a sequela of acute lung injury induced by COVID-19 (Pan et al., 2020; Schwensen et al., 2020; Tian et al., 2020; Zhou et al., 2020). Besides, in COVID-19, serum levels of pro-

**Table 2**  
Secondary endpoints.

	Control N = 30	Nintedanib N = 30	P Value
Ventilator-free days within 28 days	12 (0–17)	17 (0–21)	0.038
Percentage of high-attenuation areas on CT			
Induction of mechanical ventilation (%)	29.1 (20.3–33.1)	30.8 (20.9–46.7)	0.651
Liberation from mechanical ventilation (%)	38.7 (20.9–45.6)	25.7 (9.4–34.6)	0.027
Gastrointestinal adverse events			
Mild events	27 (90%)	25 (83.3%)	0.448
Moderate events	6 (20%)	9 (30%)	0.371
Severe events	3 (10%)	2 (6.7%)	0.640
Acute liver failure			
Mild	20 (66.7%)	24 (80%)	0.243
Moderate	6 (20%)	11 (36.7%)	0.158
Severe	2 (6.7%)	2 (6.7%)	1.00

CT, computed tomography.



**Figure 3.** Time series alterations in PaO<sub>2</sub>/FiO<sub>2</sub> (P/F) ratio in the nintedanib and control groups. Regression line with 95% confidence interval (CI) in each group estimated by multilevel mixed-effects regression model with a two-way interaction term between the group and time series. The solid black lines represent patients in the nintedanib group, and the dotted black lines represent patients in the control group. Median and 95% CI of the P/F ratio at each time point are also indicated by box and whisker plots.

inflammatory and pro-fibrotic mediators such as monocyte-1 chemoattractant protein, transforming growth factor 1, tumor necrosis factor α, fibroblast growth factor, platelet-derived growth factor, interleukin-1b and interleukin-6 were reported to be highly increased to the same levels as those in IPF (Nile et al., 2020; Xiong et al., 2020; Yuki et al., 2020). The similar cytokine profiles in IPF and COVID-19 suggested analogous mechanisms of pulmonary fibrosis in these diseases; therefore, nintedanib, which was shown to be useful in the treatment of IPF, could potentially be beneficial for severe COVID-19 patients (Lechowicz et al., 2020).

In the present study, the nintedanib group had a significantly higher P/F ratio, shorter lengths of mechanical ventilation and lower volume of high-attenuation areas on CT images. These findings clearly suggested that the administration of nintedanib could ameliorate the lung injury induced by COVID-19, potentially by modulating the progression of pulmonary fibrosis. Furthermore, the findings of CT volumetry suggested that nintedanib could minimize the long-term sequelae of COVID-19 on respiratory function, which have become an increasingly recognized and troubling health problem all over the world (WHO Coronavirus Disease Dashboard, 2021).

*Effect of nintedanib on mortality*

Despite the favorable effects of nintedanib on respiratory function, the 28-day mortality rate was not significantly different between the 2 groups. Possible explanations for these conflicting results might be attributable to the supposition that attenuating pulmonary fibrosis with nintedanib might not contribute to

reducing acute-phase deaths because pulmonary fibrosis is a late pathological finding associated with late death. In a cohort study of 159 autopsies of patients with ARDS, pulmonary fibrosis had developed in 4% of the patients with a disease duration of less than 1 week, 24% of those with a disease duration of between 1 and 3 weeks, and 61% of those with a disease duration of greater than 3 weeks (Thille et al., 2013). The results of the present study suggested that pulmonary fibrosis could develop early in the course of ARDS but could also be largely associated with patient survival in a later phase. Further clinical trials focusing on long-term mortality need to be performed.

*Safety of nintedanib*

Major side effects of nintedanib were reported to include liver problems, diarrhea, nausea, vomiting, heart attack, stroke, bleeding problems and tears (perforation) in the stomach or intestinal wall (Safety and Side Effects of OFEV, 2021). The present study thus recorded gastrointestinal and liver dysfunctions as possible adverse events that could be increased by the administration of nintedanib. However, there were no significant differences between the 2 groups in the incidence of mild, moderate and severe gastrointestinal and liver adverse events.

In a previous study of patients with IPF, the rates of diarrhea, the most frequent adverse event, were significantly higher in the nintedanib versus non-nintedanib group (61.5% vs 18.6%) (Richeldi et al., 2011). The reason for the divergent findings between the previous and present studies might be attributable to the difference in disease severity and baseline risk of adverse events.

In other words, gastrointestinal adverse events, including diarrhea, commonly complicate ICU patients requiring mechanical ventilation, and thus an additional harming effect from the administration of nintedanib might be concealed.

### Limitations

We acknowledge several limitations regarding the present study design. First, this study is not a randomized controlled trial, and we compared the nintedanib group with a historical control group. Therefore, multiple unmeasured confounding variables might account for the outcome differences observed. Second, the number of patients included in this study was small, which might lead to higher variability of the study results and potential undercoverage bias. Third, the single-center design potentially caused a sampling bias in terms of generalizability, i.e., only one specific population with COVID-19 might be included in this study. To resolve these imbalances, further large-scale multicenter randomized trials are needed to thoroughly evaluate the effects of nintedanib on the treatment of patients with severe COVID-19.

### Conclusion

In the present study, the administration of nintedanib, a new antifibrotic agent, to patients with severe COVID-19 undergoing mechanical ventilation was associated with a higher P/F ratio, shorter length of mechanical ventilation time and lower volume of high-attenuation areas on CT imaging. The use of nintedanib may offer potential benefits for minimizing the lung injury induced by COVID-19.

### Ethics approval and consent to participate

This trial was conducted in accordance with the principles of the Declaration of Helsinki and the Japanese Clinical Trials Act (Act No. 16 of April 14, 2017). The trial protocol was approved by the Institutional Review Board for Clinical Research of Osaka General Medical center as a specified clinical trial (IRB No. S202004004) and is available at the Japanese Registry of Clinical Trials (jRCTs051200036). Before study entry, written informed consent was obtained from all patients who received nintedanib.

### Consent for publication

Informed consent for publication was obtained from all the participants.

### Availability of data and materials

The statistical codes and full dataset are available from the corresponding author.

### Competing interests

The authors declare that they have no competing interests.

### Funding

This clinical study was supported by institutional funding for research projects in Osaka General Medical Center.

### Authors' contributions

Y. Umemura conceived and designed this study; contributed to acquisition, analysis and interpretation of the data; and was responsible for drafting, editing and submission of the

manuscript. Y. Mitsuyama and K. Minami contributed to the study design and conducted the segmentation of the high-attenuation areas for CT volumetry. N. Okada contributed to the study design and calculated the volumes of high-attenuation areas. K. Yamakawa contributed to the study design; acquisition, analysis and interpretation of the data; and drafting of the manuscript. K. Nochioka had a significant influence on the study design. T. Nishida, A. Watanabe and S. Fujimi contributed to the interpretation of the data and critical appraisal of the manuscript. All of the authors reviewed, discussed, and approved the final manuscript.

### Acknowledgements

The authors thank all the emergency medical service personnel, nurses, and physicians who have confronted the COVID-19 outbreak and the patients who contributed to this study.

### Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.ijid.2021.05.055>.

### References

- Auld SC, Caridi-Scheible M, Blum JM, et al. Emory COVID-19 Quality and Clinical Research Collaborative: ICU and ventilator mortality among critically ill adults with coronavirus disease 2019. *Crit Care Med* 2020;48:e799–804.
- Burki TK. Coronavirus in China. *Lancet Respir Med* 2020;8:238.
- Distler O, Highland KB, Gahlemann M, et al. Nintedanib for systemic sclerosis-associated interstitial lung disease. *N Engl J Med* 2019;380:2518–28.
- Hertzog MA. Considerations in determining sample size for pilot studies. *Res Nurs Health* 2008;31:180–91.
- Lechowicz K, Drożdżal S, Machaj F, et al. COVID-19: the potential treatment of pulmonary fibrosis associated with SARS-CoV-2 infection. *J Clin Med* 2020;9:1917.
- Nile SH, Nile A, Qiu J, et al. COVID-19: pathogenesis, cytokine storm and therapeutic potential of interferons. *Cytokine Growth Factor Rev* 2020;53:66–70.
- Pan Y, Guan H, Zhou S, et al. Initial CT findings and temporal changes in patients with the novel coronavirus pneumonia (2019-nCoV): a study of 63 patients in Wuhan, China. *Eur Radiol* 2020;30:3306–9.
- Ramos LF, Shintani A, Ikizler TA, et al. Oxidative stress and inflammation are associated with adiposity in moderate to severe CKD. *J Am Soc Nephrol* 2008;19:593–9.
- Redente EF, Aguilar MA, Black BP, et al. Nintedanib reduces pulmonary fibrosis in a model of rheumatoid arthritis-associated interstitial lung disease. *Am J Physiol Lung Cell Mol Physiol* 2018;314:L998–L1009.
- Richeldi L, Costabel U, Selman M, et al. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. *N Engl J Med* 2011;365:1079–87.
- Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med* 2014;370:2071–82.
- Safety and Side Effects of OFEV. Available at: <https://www.ofev.com/taking-ofev/side-effects>. [Accessed 25 February 2021].
- Schwensen HF, Borreschmidt LK, Storgaard M, et al. Fatal pulmonary fibrosis: a post-COVID-19 autopsy case. *J Clin Pathol* 2020;(July) jclinpath-2020-206879.
- Sime PJ, O'Reilly KM. Fibrosis of the lung and other tissues: new concepts in pathogenesis and treatment. *Clin Immunol* 2001;99:308–19.
- Sinha P, Calfee CS, Cheria S, et al. Prevalence of phenotypes of acute respiratory distress syndrome in critically ill patients with COVID-19: a prospective observational study. *Lancet Respir Med* 2020;8:1209–18.
- The National Institutes of Health. COVID-19 treatment guidelines. 2021 Available at: <https://www.nih.gov/coronavirus>. [Accessed 15 February 2021].
- Thille AW, Esteban A, Fernández-Segoviano P, et al. Chronology of histological lesions in acute respiratory distress syndrome with diffuse alveolar damage: a prospective cohort study of clinical autopsies. *Lancet Respir Med* 2013;1:395–401.
- Tian S, Xiong Y, Liu H, et al. Pathological study of the 2019 novel coronavirus disease (COVID-19) through postmortem core biopsies. *Mod Pathol* 2020;33:1007–14.
- Tomashefski Jr JF. Pulmonary pathology of acute respiratory distress syndrome. *Clin Chest Med* 2000;21:435–66.
- Viechtbauer W, Smits L, Kotz D, et al. A simple formula for the calculation of sample size in pilot studies. *J Clin Epidemiol* 2015;68:1375–9.
- WHO Coronavirus Disease (COVID-19) Dashboard. Available at: <https://covid19.who.int/>. [Accessed 15 February 2021].
- Wollin L, Maillet I, Quesniaux V, et al. Antifibrotic and anti-inflammatory activity of the tyrosine kinase inhibitor nintedanib in experimental models of lung fibrosis. *J Pharmacol Exp Ther* 2014;349:209–20.
- Wollin L, Wex E, Pautsch A, et al. Mode of action of nintedanib in the treatment of idiopathic pulmonary fibrosis. *Eur Respir J* 2015;45:1434–45.

- World Health Organization. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected: interim guidance. 2021 Available at: [https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-\(ncov\)-infection-is-suspected](https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected). [Accessed 15 February 2021].
- Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med* 2020;180:934–43.
- Xiong Y, Liu Y, Cao L, et al. Transcriptomic characteristics of bronchoalveolar lavage fluid and peripheral blood mononuclear cells in COVID-19 patients. *Emerg Microbes Infect* 2020;9:761–70.
- Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: a review. *Clin Immunol* 2020;215:108427.
- Zhou S, Wang Y, Zhu T, et al. CT features of coronavirus disease 2019 (COVID-19) pneumonia in 62 patients in Wuhan, China. *AJR Am J Roentgenol* 2020;214:1287–94.
- Zhu N, Zhang D, Wang W, et al. China novel coronavirus investigating and research team. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med* 2020;382:727–33.