Journal of Cardiovascular Disease Research
ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 08, 2024

NINTEDANIB AS A GAME CHANGER IN YOUNG AND MIDDLE AGED COVID-19 PATIENTS

Dr. Arun Kumar U[1*], Dr. Hemavathi U[2], Dr. Hamsa K[3], Dr. Lakshmi U[4], Dr. Mahendra K[5], Dr. Abhijit[6]

[1]MD General Medicine, Subbaiah Institute of Medical Sciences, Shivamogga.
[2]MS Orthodontics, Baptist hospital, Bangalore.
[3]MDRD Radiologist, AJ Institute of Medical Sciences, Mangalore.
[4]MS Obstetrics and Gynaecologist, Subbaiah Institute of Medical Sciences, Shivamogga.
[5]Diploma in Pediatrics, Neonatalogist, Subbaiah Institute of Medical Sciences, Shivamogga.
[6]MBBS, Subbaiah Institute of Medical Sciences, Shivamogga.

Corresponding Author: Dr. Arun Kumar U
MD General Medicine, Subbaiah Institute of Medical Sciences, Shivamogga.

Abstract:

Background: Pulmonary fibrosis is one of the most significant indicators of a bad prognosis in COVID-19 patients. A novel antifibrotic medication called Nintedanib inhibits several growth factors to prevent neo-angiogenesis while interfering with pulmonary fibrosis processes. The purpose of this research was to look at Nintedanib's efficacy and safety in treating young to middle-aged COVID-19 when Nintedanib is administered as a prophylactic measure.

Methodology: This case-control study included 50 COVID-19 confirmed cases, and 50 matched controls admitted at ICU and HDU. The primary endpoint was to assess the oxygen requirement and PaO2/FiO2 ratio among the two groups. Additionally, prognostic laboratory markers including Ferritin, CRP, D-dimer was assessed on days 0, 4, 11 and 15 days. 15-day mortality was determined. Appropriate statistical tests were used for comparison.

Results: During the baseline visit, PaO2/FiO2 ratio in case (56.6 ± 34.1) and control (71.16 ± 37.7) with a statistical increase in control group ($p=0.04$). However, on day 11 and day 15, the PaO2/FiO2 ratio was statistically higher in case group ($P<0.05$). The oxygen requirement over the follow-up visits in case-group statistically decreased. Except for the baseline, at all follow-up visits, the levels of ferritin, CRP, D-dimer were statistically lower in the case group compared to control group ($p<0.05$). Additionally, a statistical increase in the mortality in control group was noted at 15^{th} day of the study.

Conclusion: Nintedanib treatment has the potential to reduce lung damage in COVID-19 patients and to assist COVID-19 patients prophylactically while disease is active.

Keywords: Pulmonary fibrosis, Wnt/β-catenin, tyrosine-kinase, D-dimer, Ferritin.

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus that causes the highly infectious coronavirus disease 2019 (COVID-19).Since December 2019, when the first cases were discovered in Wuhan, China, the COVID-19 has spread quickly over the globe[1].From minor upper respiratory tract symptoms to severe acute respiratory distress syndrome, the symptoms of COVID-19 infection range[2].

As of May 31, 2021, the number of COVID-19 cases worldwide surpassed 171 million, resulting in the loss of almost 3.69 million lives. India is ranked second in terms of the total cumulative COVID-19 cases and shares around 16% of the reported worldwide burden of cases. In terms of the overall number of deaths caused by COVID-19, India is ranked third worldwide with 334 608 deaths[3].Between US $77 billion and US $2.7 trillion was the predicted global economic cost of COVID-19 in 2019[4].

Beyond the early reports of individuals experiencing weariness for months after contracting the virus, long-haul COVID-19 has come to be associated with a variety of problems and potential aftereffects. Numerous late consequences related to COVID-19 infection have been identified by prior research. These issues include lung fibrosis, venous thromboembolism (VTE), arterial thromboses, heart thrombosis and inflammation, stroke, dermatological problems, and general mood disorders[5].

The pulmonary damage caused by SARS-CoV-2 is caused by many ways. Numerous alterations brought on by an acute infection have the potential to promote fibrosis. Viral entrance into cells directly causes cell death, which in turn causes an increase in proinflammatory cytokines. This is especially true of type II alveolar epithelial cells, which maintain the epithelial barrier. Diffuse alveolar damage as a result attracts neutrophils, macrophages, and lymphocytes, which in turn attract fibroblasts, which eventually lead to fibrosis[6].

Despite the fact that a number of pharmacotherapies were tried in the management of COVID-19, a gap in the therapy was observed because of the virus's characteristics, the rising case load, the associated morbidity and mortality, the lack of knowledge about the disease's pathology, an array of symptoms and complications, as well as the drug's side effects and cost.

The Food and Drug Administration (FDA) first licensed the tyrosine kinase inhibitor Nintedanib in 2014 for the treatment of idiopathic pulmonary fibrosis (IPF). Additional indications include progressive phenotypic interstitial lung disease because of its anti-fibrotic properties and interstitial lung disease related with systemic sclerosisIt has been demonstrated that a key regulatory mechanism in adult organ repair is wnt/b-catenin signalling. The canonical Wnt/b-catenin pathway involves ligand binding causing cytoplasmic b-catenin to accumulate in the nucleus. This allows b-catenin to bind to transcriptional binding sequences T-cell factor (TCF)/lymphocyte enhance factor (LEF) and regulate transcription of downstream genes. When homeostasis is maintained, b-catenin is drawn to the membrane in response to signals of cell-to-cell or cell-matrix contact by interacting with E-cadherin (E-Cad). The b-catenin Y654 residue is phosphorylated by Src kinase under stimulation by hepatocyte growth factor (HGF) or transforming growth factor-b (TGF-b). Subsequently, it separates from E-Cad and moves into the nucleus, where it facilitates fibrogenesis. Nintedanib is known to halt the pathway[7].

A review of the literature found little information about the safety and efficacy of Nintedanib as a new anti-fibrotic therapy in young to middle-aged COVID-19 patients worldwide. The study additionally aimed to assess the improvement in patients who are on non-invasive ventilation and prognostic markers like D-dimer, C-reactive protein and ferritin. The current study was therefore designed.

The current study is unique as it included patients with confirmed COVID-19 infections and administered to them Ninitedanib as a prophylactic strategy. On the other hand, individuals with COVID-19 pulmonary fibrosis have received Nintedanib in other studies available in the literature.

MATERIALS AND METHODS

Between April and June of 2021, case-control research was carried out at the Subbaih Medical College in Shivamogga, Karnataka. 100 individuals of either sex, ranging in age from 20 to 65, who tested positive for COVID-19admitted in Intensive Care Unit (ICU) and High Dependency oxygen Units (HDU) were included in the research. Patients with concomitant conditions such as diabetes, hypertension, chronic renal disease, malignancy, history of cerebro-vascular accident, any immunosuppressive disease and prolonged COVID-

19 were excluded. The study commenced after receiving approval from Institutional Ethics Committee and written informed consent was obtained from all the patients.

All the included participants received a standard regimen including multivitamins, Proton pump inhibitors, corticosteroids were administered. In addition to the standard regimen, participants in case-group including 50 patients, were administered with Nintedanib 100-200mg twice daily for 15 days. Clinico-demographic data, requirement of oxygen and laboratory tests (ferritin level, D-dimer, C-reactive protein) was noted on days 0, 4, 11 and 15.

The primary outcome of the study was to assess the oxygen requirement and P:F ratio. The secondary endpoint was the change in ferritin, CRP and D-dimer levels after the therapy in both the groups.

Statistical analysis:

The data was gathered and analyzed using Microsoft excel (Version 16.87). Quantitative data was presented with the help of Mean and Standard deviation, while qualitative data was represented as frequencies and percentages. The comparison between groups was made by employing Unpaired T-test/ Mann-Whitney U test based on the normality of the data. Categorical data was compared using Chi-square test/ Fischer exact test. $P<0.05$ was deemed statistically significant.

RESULTS AND OBSERVATIONS

A total of 50 patients who were administered with Nintedanib, and 50 matched controls were included in the study. The mean age of the case-group was 48.32 ± 11.7 years and control group were47.14 ± 11.6 years with p=0.3. Hence, no statistical difference was seen in age between the two groups. Table 1 describes the clinico-demographic details. There was no statistical difference between the groups in terms of age distribution, gender distribution, distribution of co-morbidities ($p>0.05$ on Chi-square test).

Clinico-demographic parameters	**Case (n=50)**	**Control (n=50)**	**P-value**
Age in years (Mean ± SD)	48.32 ± 11.7	47.14 ± 11.6	0.3
Gender distribution			

Male	30	33	0.53
Female	20	17	
Distribution of Co-morbidities			
Asthma	29	27	0.6
Diabetes mellitus	35	36	0.8
Hypertension	32	34	0.6
Ischemic heart disease	11	13	0.6
Years of respiratory comorbidities (Mean ± SD)	7.5 ± 3.8	6.94 ± 3.8	0.23

Table 1: Distribution and comparison of clinico-demographic details.

Oxygen requirement and PaO2/FiO2 ratio:

One of the important objectives of the study was to assess thePaO2/FiO2 and laboratory parameters between the groups at days 0, 4, 11 and 15 days.

PaO2/FiO2 ratio	**Day 0**	**Day 4**	**Day 11**	**Day 15**
Case (n=50)	56.6 ± 34.1	66.36 ± 9.7	60.4 ± 26.5	88.6 ± 71.8
Control (n=50)	71.16 ± 37.7	67.8 ± 6.6	37.7 ± 9.9	22.2 ± 9.01
P-value	0.04*	0.3	0.0001*	0.0001*

Table 2: Comparison of PaO2/ FiO2 ratio. **p<0.05 on unpaired T-test is significant.*

The study found that during the baseline visit, PaO2/FiO2 ratioin case group was 56.6 ± 34.1 and in control group was 71.16 ± 37.7 with a statistical increase in control group (p=0.04). No statistical difference in the PaO2/FiO2 ratio was seen on day 4. However, on day 11 and day 15, the PaO2/FiO2 ratio was statistically higher in case group (P<0.05).

The oxygen requirement over the follow-up visits in case-group statistically decreased with p<0.05 on repeated measures ANOVA.

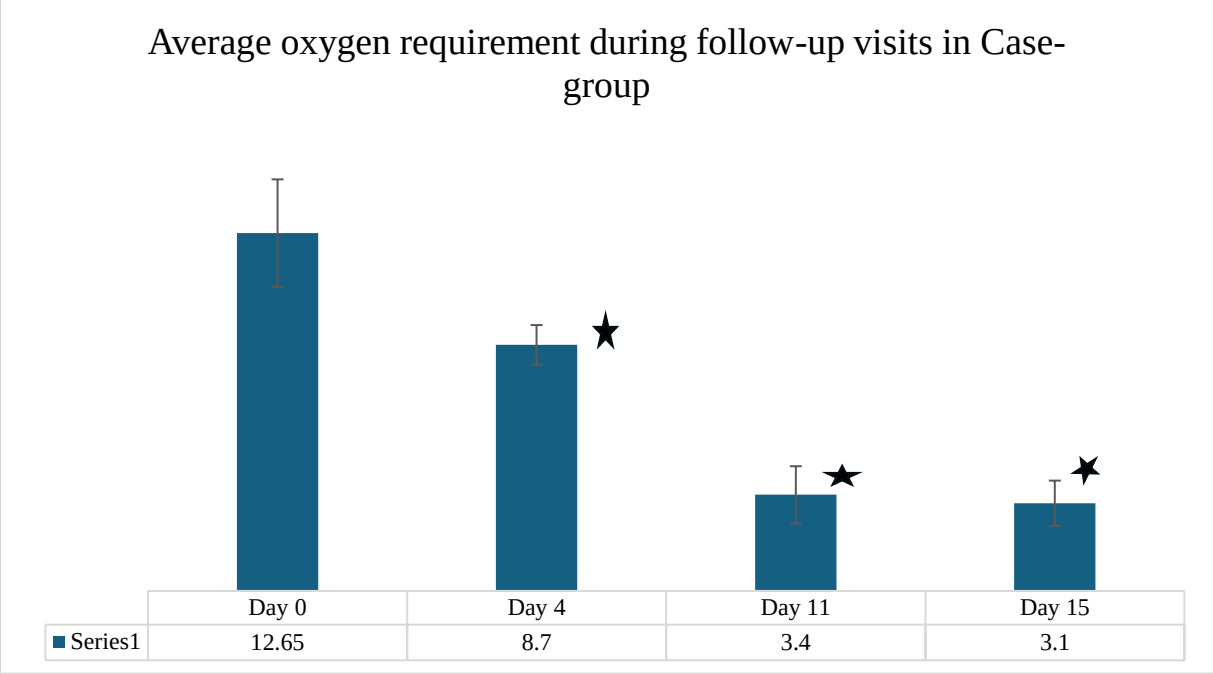

Figure 1: Average oxygen requirement during follow-up visits in Case-group.

**Represents statistical decrease with p<0.05 on Repeated measures ANOVA compared to day 0.*

Laboratory parameters:

The purpose of the study was to evaluate the change in laboratory markers on consecutive follow-up visits, such as ferritin, CRP, and D-dimer levels. The same is shown in table 3.

	Ferritin (ng/mL)			**CRP (in mg/dL)**			**D-dimer**		
Days	**Case (n=50)**	**Control (n=50)**	**P-value**	**Case (n=50)**	**Control (n=50)**	**P-value**	**Case (n=50)**	**Control (n=50)**	**P-value**
Day 0	430 [370-480]	200 [160-577.5]	**0.01***	250 [215-280]	180 [160-320]	**0.3**	7250 [4800-8475]	4000 [3800-8200]	**<0.05***
Day 4	180 [160-335]	400 [380-800]	**<0.05***	180 [160-267.5]	300 [290-430]	**<0.05***	3900 [3350-6275]	7000 [5900-9250]	**<0.05***

Day 11	120 [115-500]	580 [540-640]	**<0.05***	70 [65-300]	360 [320-380]	**<0.05***	850 [750-8000]	8700 [8400-8800]	**<0.05***
Day 15	50 [40-750]	900 [850-950]	**<0.05***	6 [5-410]	445 [430-470]	**<0.05***	180 [100-9300]	9800 [9500-10000]	**<0.05***

Table 3: Comparison of laboratory parameters between the groups on follow-up visits.

**p<0.05 on unpaired T-test is significant.*

It was seen that ferritin level; CRP level; D-dimer was statistically higher in case group on day 0. However, thereafter on day 4, day 11 and day 15 there was astatistically increasing trend in ferritin levels in control group (p<0.05 on unpaired T test).

Number of Mortality:

At every visit, the total number of fatalities in both groups was recorded. There was no mortality seen in either group on day 0. Nevertheless, five patients in the case group and twenty-eight patients in the control group passed away on days four and eleven. On day 15, it was seen that COVID-19 problems had claimed the lives of 17 individuals in the case group and 40 patients in the control group. A statistically significant increase in deaths was seen in the control group (p<0.05 on chi-square test).

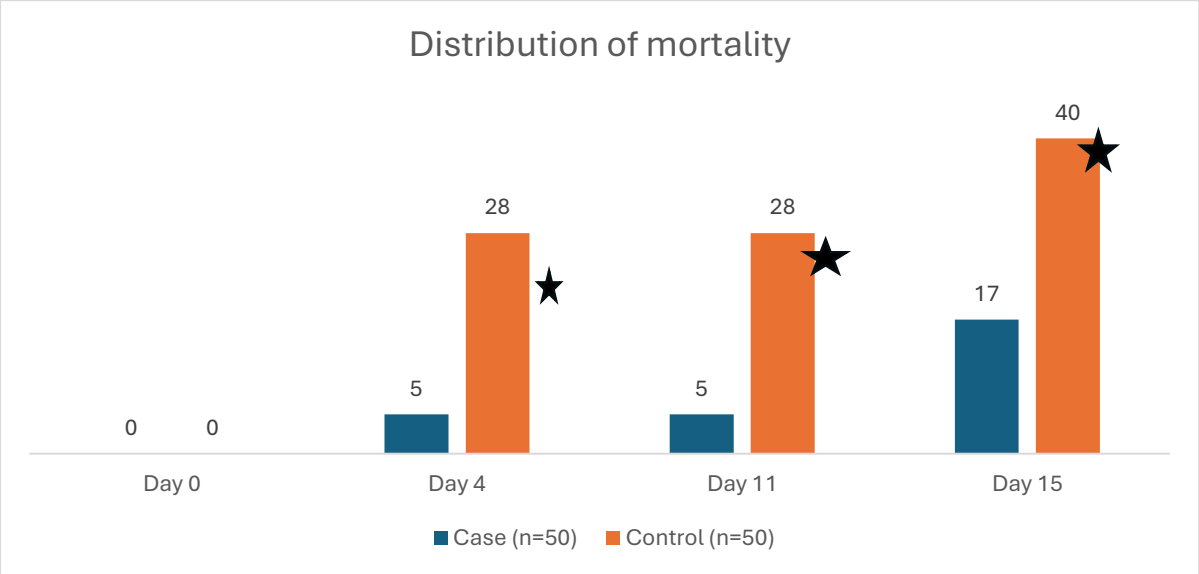

Figure 2: Distribution of mortality in both groups. **p<0.05 on Chi-square-test is significant.*

DISCUSSION

This is among the first studies to assess Nintedanib's efficacy and safety in COVID-19 pulmonary fibrosis patients. According to the current study, Nintedanib increased the PaO2/FiO2 ratio and decreased the oxygen requirement over the period. The study also revealed that, throughout the follow-up and when compared to the control group, Nintedanib significantly decreased the levels of ferritin, CRP, and D-dimer.However, the baseline laboratory readings were significantly higher in case group attributed to the disease severity. Furthermore, individuals receiving Nintedanib saw a decreased rate of death.

Numerous studies evaluating the efficacy of Nintedanib in treatment individuals with idiopathic pulmonary fibrosis have been conducted in the past. Trials such as TOMORROW [8]and INPULSIS [9]are considered landmark trials.The limitation of neo-angiogenesis by the inhibition of many growth factors, including Fibroblast growth factor receptor (FGFR), Vascular endothelial growth factor receptor (VEGFR), Platelet-derived growth factor receptor (PDGFR), Colony-stimulating factor-1-receptor (CSF1R), and Fms-like tyrosine kinase-3 (FLT3), is the proposed mechanism of action[7, 10–13].

Retrospective matched case-control research was carried out in Thailand by Saiphoklang N et al[14] in accordance with the current study. SpO2/FiO2 ratio was enhanced by Nintedanib over the follow-up. The Nintedanib group's baseline SpO2/FiO2 ratio was noticeably lower, indicating the severity of the illness.Nevertheless, there were no variations in the oxygen improvement between the Nintedanib and control groups. However, the results of our investigation showed that Ninitedanib had a decreased oxygen need owing to improved PaO2/FiO2 ratio. Also, the administration of Nintedanib was started from day-0 of the diagnosis.

Unlike Saiphoklang N et al[14] and Ogata and colleagues[15], we did not assess the chest X-ray changes in the included study participants as the study was conducted for a shorter duration of 15 days. According to research by Ogata and colleagues[15], individuals with post-COVID-19 lung fibrosis were able to have improved chest radiographs following three months of antifibrotic medication.

Procalcitonin (PCT), D-dimer, hyperferritinemia, and increased blood levels of CRP are markers of hyperinflammation that are increasingly seen in critically ill patients. These results imply that a cytokine storm may play a critical role in the pathogenesis of COVID-19[16].Utilizing these lab indicators to gauge Nintedanib's effectiveness is a novel approach

to this research.When compared to the control group, these parameters in the current study significantly decreased over the follow-up. Its severity was highlighted, nonetheless, by the observation that the Day 0 case group's baseline values for these laboratory markers were greater.This demonstrates how the study drug-Nintedanib works to improve clinical outcomes by lowering inflammation linked to lung fibrosis.

In contrast with Saiphoklang N et al[14] and Umemura Y et al [17], the current study found a decreased fatalities among patients administered with Nintedanib from day 0. This throws light on the safety and improved clinical outcome of the drug. One explanation for these contradictory results is thatthe idea that Nintedanib, because pulmonary fibrosis is a late pathological feature associated with late mortality, it is possible that attenuating pulmonary fibrosis with Nintedanib will not contribute to lowering acute-phase fatalities. Furthermore, it was seen that mortality was higher in patients with comorbid conditions in both the groups.

The limitations of the study include its single-centered nature which could affect the generalizability of the study outcomes. Furthermore, because the trial was short-term, we were unable to use chest imaging investigates to evaluate the long-term effects. Additionally, adverse events linked to therapy were not identified.

CONCLUSION

In summary, Nintedanib may offer a unique therapeutic strategy for the treatment of COVID-19 pulmonary fibrosis.The COVID-19 pandemic's magnitude and the amount of people requiring invasive ventilation globally are making post-COVID-19 pulmonary fibrosis a deadly menace to public health.Over the course of the follow-up, the study demonstrated that Nintedanib had dramatically reduced the levels of ferritin, CRP, D-dimer, and oxygen need. Nintedanib was also linked to a decreased rate of fatalities. Hence, compared to non-drug users, Ninitedanib is more effective and has a better prognosis in COVID-19 patients. Nintedanib not only helps in post fibrosis of COVID-19, but it also helps prophylactically in COVID-19 patients when actively suffering the disease.

Source of funding: Nil

Acknowledgement: Nil

Conflicts of interest: Nil

REFERENCES

1. Cascella M, Rajnik M, Aleem A, et al. Features, Evaluation, and Treatment of Coronavirus (COVID-19) [Updated 2023 Aug 18]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554776/
2. Aguilar RB, Hardigan P, Mayi B, Sider D, et al. Current Understanding of COVID-19 Clinical Course and Investigational Treatments. Front Med (Lausanne). 2020 Oct 21;7:555301.
3. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis [Internet]. 2020;20(5):533–4.
4. Forsythe S, Cohen J, Neumann P, Bertozzi SM, Kinghorn A. The economic and public health imperatives around making potential coronavirus disease–2019 treatments available and affordable. Value Health. 2020;23(11):1427–1431.
5. SeyedAlinaghi S, Afsahi AM, MohsseniPour M, et al. Late Complications of COVID-19; a Systematic Review of Current Evidence. Arch AcadEmerg Med. 2021 Jan 20;9(1):e14.
6. McDonald LT. Healing after COVID-19: are survivors at risk for pulmonary fibrosis? Am J Physiol Lung Cell Mol Physiol 320: L257–L265, 2021.
7. Li X, Liu X, Deng R, Gao S, et al. Nintedanib Inhibits Wnt3a-Induced Myofibroblast Activation by Suppressing the Src/β-Catenin Pathway. Front Pharmacol. 2020 Mar 16;11:310.
8. Richeldi L, Costabel U, Selman M, Kim DS, et al. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. N Engl J Med. 2011 Sep 22;365(12):1079-87.
9. Richeldi L, du Bois RM, Raghu G, Azuma A, et al; INPULSIS Trial Investigators. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014 May 29;370(22):2071-82. doi: 10.1056/NEJMoa1402584. Epub 2014 May 18. Erratum in: N Engl J Med. 2015 Aug 20;373(8):782.
10. Hostettler KE, Zhong J, Papakonstantinou E, et al. Anti-fibrotic effects of nintedanib in lung fibroblasts derived from patients with idiopathic pulmonary fibrosis. Respir Res. 2014 Dec 12;15(1):157.
11. Hajari Case A, Johnson P. Clinical use of nintedanib in patients with idiopathic pulmonary fibrosis. BMJ Open Respir Res. 2017 Jun 28;4(1):e000192.

12. Wollin L, Wex E, Pautsch A, Schnapp G, Hostettler KE, et al. Mode of action of nintedanib in the treatment of idiopathic pulmonary fibrosis. Eur Respir J. 2015 May;45(5):1434-45.
13. Gole S, Bankole A. Nintedanib. [Updated 2023 Jun 15]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK585049/#
14. Saiphoklang N, Patanayindee P, Ruchiwit P. The Effect of Nintedanib in Post-COVID-19 Lung Fibrosis: An Observational Study. Crit Care Res Pract. 2022 Sep 26;2022:9972846.
15. Ogata H, Nakagawa T, Sakoda S, Ishimatsu A, Taguchi K, Kadowaki M, Moriwaki A, Yoshida M. Nintedanib treatment for pulmonary fibrosis after coronavirus disease 2019. Respirol Case Rep. 2021 Mar 30;9(5):e00744.
16. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020 Mar 28;395(10229):1033-1034.
17. Umemura Y, Mitsuyama Y, Minami K, Nishida T, et al. Efficacy and safety of nintedanib for pulmonary fibrosis in severe pneumonia induced by COVID-19: An interventional study. Int J Infect Dis. 2021 Jul;108:454-460.