Dear Reviewers:

Thank you for your professional and kind comments on our manuscript entitled "Strengthening Pharmacotherapy Research for COVID-19-Induced Pulmonary Fibrosis" (ID: 05307734). These comments are all valuable and very helpful for revising and improving our manuscript. We have studied the comments carefully and have made corrections as you suggested. The responses to your comments are as follows:

Comments to Authors from Reviewer 1:

It would be interesting to read specific considerations to test the hypotheses, esp. concerning the different pharmacological pathways in different cultures/ethnic groups, e.g., middle European liver function could be different to caucasian, or differences concerning sex, genetics,,...etc.

Answer:

Thank you for your thoughtful and professional recommendation. Following your suggestion, we conducted an extensive search for pertinent information, primarily focusing on nintedanib. It is indicated that within the inter-patient variability range of nintedanib exposure, it demonstrates similar therapeutic effects among both Asian and White individuals[1, 2]. Additionally, it is noteworthy that sex does not influence nintedanib pharmacokinetics[1].

In addition, in COVID-19-induced pulmonary fibrosis, there have been findings of telomerase reverse transcriptase (TERT) and mucin 5B (MUC5B) mutations, which are well-known genetic risk factors for the condition[3, 4]. However, researches on the genetic risk factors specific to COVID-19-induced pulmonary fibrosis and related drug treatments are currently limited. Therefore, in our revised manuscript, we briefly mention the important information that has already been published.

In response to your guidance, we have incorporated a dedicated section titled "PHARMACOLOGICAL CONSIDERATIONS ON ANTI-FIBROSIS TREATMENT FOR COVID-19-INDUCED PULMONARY FIBROSIS" into the revised manuscript. The revised content is as follows:

When testing the effects of pharmacotherapy for COVID-19-induced pulmonary fibrosis, it is crucial to consider pharmacological factors. Studies have demonstrated that nintedanib exhibits comparable therapeutic effects across various ethnic groups, including Asian and White patients[1, 2]. Additionally, the literature finding also confirm that gender has no noticeable effect on nintedanib pharmacokinetics[1]. In terms of the utilization of anti-fibrotic treatment, Black patients are 40% less likely than their White counterparts to receive such treatment, and similarly, female patients are 59% less likely than their male counterparts[5].

These findings offer valuable insights into potential disparities in the administration of anti-fibrotic treatment, highlighting the importance and potential significance of race and gender factors. Further research in this area holds great promise for exploring and understanding these disparities in greater detail, which can contribute to the development of more personalized and equitable treatment approaches. Additionally, investigating the influence of race and gender on the effectiveness and safety profiles of anti-fibrotic therapies can provide a deeper understanding of their impact on different patient populations, ultimately leading to improved healthcare outcomes for all individuals.

In individuals with telomerase reverse transcriptase (TERT) mutations, there may be an increased risk of developing COVID-19-induced pulmonary fibrosis[3]. It has also been observed that TERT/TERC mutations are resistant to pirfenidone therapy[6]. Additionally, other genetic variants such as MUC5B, DPP9, and ATP11A have been associated with COVID-19-induced pulmonary fibrosis[4]. Exploring the role of genetics in this condition may pave the way for the development of novel agents for targeted therapy and personalized treatment.

Once again, we appreciate your valuable input and are confident that these additions enhance the comprehensiveness of our manuscript.

1 **Wind S**, Schmid U, Freiwald M, Marzin K, Lotz R, Ebner T, Stopfer P, Dallinger C. Clinical Pharmacokinetics and Pharmacodynamics of Nintedanib. *Clin Pharmacokinet* 2019; **58**: 1131-1147 [PMID: 31016670 DOI: 10.1007/s40262-019-00766-0]

2 **Taniguchi H**, Xu Z, Azuma A, Inoue Y, Li H, Fujimoto T, Bailes Z, Schlenker-Herceg R, Kim DS. Subgroup analysis of Asian patients in the INPULSIS(®) trials of nintedanib in idiopathic pulmonary fibrosis. *Respirology* 2016; **21**: 1425-1430 [PMID: 27399197 DOI: 10.1111/resp.12852]

3 **Yetkin NA**, Kiraz A, Baran Ketencioğlu B, Bol C, Tutar N. Are MUC5B and TERT mutations genetic risk factors for pulmonary fibrosis in individuals with severe COVID-19? *Tuberk Toraks* 2023; **71**: 34-40 [PMID: 36912407 DOI: 10.5578/tt.20239905]

4 **Patrucco F**, Solidoro P, Gavelli F, Apostolo D, Bellan M. Idiopathic Pulmonary Fibrosis and Post-COVID-19 Lung Fibrosis: Links and Risks. *Microorganisms* 2023; **11** [PMID: 37110318 DOI: 10.3390/microorganisms11040895]

5 **Kaul B**, Lee JS, Petersen LA, McCulloch C, Rosas IO, Bandi VD, Zhang N, DeDent AM, Collard HR, Whooley MA. Disparities in Antifibrotic Medication Utilization Among Veterans With Idiopathic Pulmonary Fibrosis. *Chest* 2023; **164**: 441-449 [PMID: 36801465 DOI: 10.1016/j.chest.2023.02.027]

6 **Ma H**, Wu X, Li Y, Xia Y. Research Progress in the Molecular Mechanisms, Therapeutic Targets, and Drug Development of Idiopathic Pulmonary Fibrosis. *Front Pharmacol* 2022; **13**: 963054 [PMID: 35935869 DOI: 10.3389/fphar.2022.963054]

Comments to Authors from Reviewer 2:

Dear authors, it is an important problem that you have treated in this manuscript. In my opinion, it better to try to suggest dosages and timing of drugs proposed for COVID 19-induced pulmonary fibrosis. Please add this informations. Very well the structure of the Editorial and the bibliographic support

Answer:

Thank you for your insightful and targeted suggestion and professional input.

(1) On timing of drugs proposed for COVID-19-induced pulmonary fibrosis.

The timing of administering anti-fibrotic drugs for patients remains a subject of ongoing debate. Divergent opinions exist, with some advocating for early and preventative treatments, while others caution against the premature use of anti-fibrotic drugs[7-9]. Each perspective is grounded in its own reasoning. Proponents of early intervention argue that COVID-19-induced pulmonary fibrosis might constitute an irreversible process. Conversely, those cautious about early treatment weigh the cost of anti-fibrosis treatment against the potential inevitability of COVID-19-induced pulmonary fibrosis. The nuances of these contrasting views underscore the complexity surrounding the optimal timing for administering anti-fibrotic drugs in the context of COVID-19-related complications.

(2) On dosages of drugs proposed for COVID-19-induced pulmonary fibrosis.

We have incorporated additional drug dosage information, including details for pirfenidone, nintedanib, N-acetylcysteine (NAC), and others. In addition，we included considerations related to dosage form.

Specifically addressing the concerns from the reviewer 2, we have introduced a new section titled "TIMING AND DOSAGES OF MEDICATIONS PROPOSED FOR COVID-19-INDUCED PULMONARY FIBROISIS" in the revised manuscript. The content is as follows:

The optimal timing of medication administration for COVID-19-induced

pulmonary fibrosis remains a topic of ongoing debate, with advocates for early and preventative approaches as well as those in favor of using anti-fibrotic drugs only when clear signs of pulmonary fibrosis with progressive exacerbations are present[7-9]. Each perspective is grounded in its own reasoning. Supporters of early intervention argue that COVID-19-induced pulmonary fibrosis might constitute an irreversible process, while those who are cautious about early treatment weigh the cost of anti-fibrosis treatment against the potential inevitability of COVID-19-induced pulmonary fibrosis. The nuances of these contrasting views underscore the complexity surrounding the optimal timing for administering anti-fibrotic drugs in the context of COVID-19-related complications. Further research on the timing of anti-fibrotic medication for pulmonary fibrosis caused by COVID-19 from both basic and clinical perspectives is necessary.

In order to achieve successful pharmacotherapy, proper dosages of promising drugs for anti-fibrosis treatment should be investigated. Table 1 summarizes the recommended dosages for some medications currently in use. Additionally, the development of novel drug delivery systems, such as inhalable systems including lipid-based nanocarriers, nanovesicles, polymeric nanocarriers, protein nanocarriers, nanosuspensions, nanoparticles, gold nanoparticles, and hydrogel, could prove to be a promising area for the treatment of pulmonary fibrosis caused by COVID-19[10].

Table 1 The recommended dosages for some medications in use

medications	**recommended dosages**
Pirfenidone	2400 mg/d for 12–24 wk[11]
Nintedanib	150 mg or 100 mg (for patients with mild hepatic impairment) twice daily[7]
N-acetylcysteine (NAC)	600 mg every 8 h, 600 mg twice daily for 14 d, and 40 mg/(kg · d) for 3 d[12]
Anakinra	a total dose of 600 mg (a loading dose of 200 mg twice

	daily, followed by 100 mg once daily for 2 d)[13]
Nimotuzumab	intravenous administration: 2-3 times with an interval of 72 h, including a loading dose of 200 mg, followed by 100 mg[14]
Vitamin D	COVID-19 patients with 25(OH)D serum levels under 20 ng/mL: 6000–7000 oral IU/d for the first 6–8 wk for correction of deficiency and 2000 to 3000 oral IU/d for maintenance[15]

We appreciate your guidance and believe that these additions contribute to the comprehensive nature of our manuscript.

7 **Hashemian SM,** Farhadi T, Varahram M, Velayati AA. Nintedanib: a review of the properties, function, and usefulness to minimize COVID-19-induced lung injury. Expert Rev Anti Infect Ther 2022, 21: 7-14 [DOI:10.1080/14787210.2023.2153116]

8 **Smelcerovic A**, Kocic G, Gajic M, Tomovic K, Djordjevic V, Stankovic-Djordjevic D, Anderluh M. DPP-4 Inhibitors in the Prevention/Treatment of Pulmonary Fibrosis, Heart and Kidney Injury Caused by COVID-19-A Therapeutic Approach of Choice in Type 2 Diabetic Patients? *Front Pharmacol* 2020; **11**: 1185 [PMID: 32848788 DOI: 10.3389/fphar.2020.01185]

9 **Chinese Research Hospital Association**; Respiratory Council. [Expert recommendations for the diagnosis and treatment of interstitial lung disease caused by novel coronavirus pneumonia]. *Zhonghua Jie He He Hu Xi Za Zhi* 2020; **43**: 827-833 [PMID: 32992435 DOI: 10.3760/cma.j.cn112147-20200326-00419]

10 **Wan Q**, Zhang X, Zhou D, Xie R, Cai Y, Zhang K, Sun X. Inhaled nano-based therapeutics for pulmonary fibrosis: recent advances and future

prospects. *J Nanobiotechnology* 2023; **21**: 215 [PMID: 37422665 DOI: 10.1186/s12951-023-01971-7]

11 **Al-Kuraishy HM**, Batiha GE, Faidah H, Al-Gareeb AI, Saad HM, Simal-Gandara J. Pirfenidone and post-Covid-19 pulmonary fibrosis: invoked again for realistic goals. *Inflammopharmacology* 2022; **30**: 2017-2026 [PMID: 36044102 DOI: 10.1007/s10787-022-01027-6]

12 **Micheletto C**, Izquierdo JL, Avdeev SN, Rada Escobar RA, Pacheco Gallego MC. N-acetylcysteine as a therapeutic approach to post-COVID-19 pulmonary fibrosis adjunctive treatment. *Eur Rev Med Pharmacol Sci* 2022; **26**: 4872-4880 [PMID: 35856379 DOI: 10.26355/eurrev_202207_29212]

13 **Nan D**, Abraira-Meriel C, de la Roz-Fernández S, Maestre-Orozco T, Hernandez JL, Fernandez-Ayala M. Delayed Use of the Recombinant Human IL-1 Receptor Antagonist Anakinra in Five COVID-19 Patients with Pulmonary Fibrosis and Persistent Hypoxaemia: A Preliminary Report. *Eur J Case Rep Intern Med* 2021; **8**: 002821 [PMID: 34790623 DOI: 10.12890/2021_002821]

14 **Londres HD**, Armada JJ, Martínez AH, Abdo Cuza AA, Sánchez YH, Rodríguez AG, Figueroa SS, Llanez Gregorich EM, Torres Lahera ML, Peire FG, González TM, González YZ, Añé Kouri AL, Palomo AG, Concepción MT, Pérez LM, Luaces-Alvarez PL, Iglesias DE, Hernández DS, Suzarte MR, Ramos TC. Blocking EGFR with nimotuzumab: a novel strategy for COVID-19 treatment. *Immunotherapy* 2022; **14**: 521-530 [PMID: 35306855 DOI: 10.2217/imt-2022-0027]

15 **Cutolo M**, Paolino S, Smith V. Evidences for a protective role of vitamin D in COVID-19. *RMD Open* 2020; **6** [PMID: 33372031 DOI: 10.1136/rmdopen-2020-001454]

We have tried our best to make changes to improve the manuscript by strictly following your professional comments and suggestions.

We appreciate your great work sincerely and hope that the correction will meet the standard for publication.

Once again, thank you very much for your professional and kind comments and suggestions.

Kind regards

Fushan Tang