Pharmacotherapy and pulmonary fibrosis risk after SARS-CoV-2 infection–response to Guangting Zeng and Yuchi Zhou

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The Lancet Regional Health - Americas 2023;26: 100611

Published Online xxx https://doi.org/10.1016/j.lana.2023.100611

We greatly appreciate Dr. Zeng and Dr. Zhou for their commentary which mentions that risk factors for post-COVID pulmonary fibrosis include advanced age, disease severity, length of ICU stay, mechanical ventilation, smoking, and chronic alcoholism, as this is well-aligned with the existing body of evidence.[1] Our study exclusively encompassed severe or critically ill hospitalized patients due to COVID-19, acknowledging inherent biases tied to severity and ICU care. However, our study design was meticulously tailored to address these confounders. We carefully adjusted for advanced age, severity of comorbid diseases, and treatments used during hospitalization (remdesivir, dexamethasone, and IL-6 inhibitors) by including them in our propensity score matching.[2] Our hypothesis was that drug exposure increased the risk of post-COVID pulmonary fibrosis in part by increasing the risk of severe acute COVID, mechanical ventilation, and ARDS. Therefore, controlling for the severity of acute COVID would bias our results towards the null as this would not represent the total-effect association of drug exposure with pulmonary fibrosis risk. We thus did not control for severity of illness, length of COVID hospitalization, or mechanical ventilation in our propensity score analysis in order to more comprehensively present the effect of drug exposure on post-COVID pulmonary fibrosis.

Further, Dr. Zeng and Dr. Zhou highlight the nuanced challenge of accurately classifying pulmonary fibrosis subtypes in clinical settings.[1] Indeed, recognizing the complexity and heterogeneity of fibrosis is essential for effective patient care.[3] While we concur on the importance of precise classification in understanding etiology, assessing risk factors, and tailoring interventions, we respectfully offer a counterpoint, based on the value and representation that a diverse range of pulmonary fibrosis subtypes brings to epidemiological analysis, especially when estimating disease incidence and risk. Focusing solely on a single subtype may inadvertently limit the scope of insights gained, as it may fail to capture the full spectrum of risk for fibrotic lung disease faced by clinicians. Our study's intent was to mirror the true heterogeneity faced in clinical practice and thus capture a representative snapshot of real-world scenarios, where various pulmonary fibrosis subtypes coexist, each with distinct challenges. This approach enriches the analysis and provides a more comprehensive understanding of the relationship between pharmacotherapy and pulmonary fibrosis risk, reflecting the diverse clinical landscapes encountered by healthcare professionals. The comments from Dr. Zeng and Dr. Zhou are, however, an important opportunity to highlight the need to explore a major question in the development of post-COVID pulmonary fibrosis, - the risk for developing the progressive pulmonary fibrosis (PPF) phenotype.[4] Patients with PPF may present with a unique trajectory of lung function decline, radiologic features of new or worsening fibrosis, and increased symptom burden with implications on quality of life and mortality.[5] We thus agree that more work is needed to optimally determine the true burden of severe SARS-CoV2 infection in patients with post-COVID pulmonary fibrosis.

We thank Dr. Zeng and Dr. Zhou again for enriching the discourse on post-COVID pulmonary fibrosis and its intricate dynamics.

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Authorship was determined using ICMJE recommendations.

DOI of original article: https://doi.org/10.1016/j.lana.2023.100590

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Disclaimer

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the N3C program.

Declaration of interests

RB, TJB, VZ, HZ, AES, and RK have nothing to disclose. AA has received speaking and advisory board fees from Genentech and Boehringer Ingelheim and is supported by a career development award from the National Heart, Lung, and Blood Institute (NHLBI K23HL146942), and grant funding from the American College of Chest Physicians and the Pulmonary Fibrosis Foundation. BKP is supported by a career development award from the NHLBI (K23-HL148387) and funding from the Walder Foundation and the Center for Healthcare Delivery Science and Innovation at the University of Chicago. WFP is supported by a career development award from the NHLBI (K08HL150291). JS has research and training funding from NIH, NSF, and the Burroughs Wellcome Fund, and has a potential financial interest in PulmOne Advanced Medical Diagnostics, Ltd, Israel. AES has equities in the following companies: Pharmaceuticals: Abbott Laboratories, Pfizer, Novo Nordisk. Industrials: in construction, IT, finance, retail, and food sectors (21 companies and 2 exchange traded funds).

Acknowledgements

The analyses described in this publication were conducted with data or tools accessed through the NCATS N3C Data Enclave https://covid.cd2h.org and N3C Attribution & Publication Policy v 1.2-2020-08-25b supported by NIH K23HL146942, NIH K08HL150291, NIH K23HL148387, NIH UL1TR002389, NCATS U24 TR002306, and a SECURED grant from the Walder Foundation/Center for Healthcare Delivery Science and Innovation, University of Chicago. WFP received a grant from the Greenwall Foundation. This research was possible because of the patients whose information is included within the data and the organizations (https://ncats.nih.gov/n3c/resources/data-contribution/data-transfer-agreement-signatories) and scientists who have contributed to the on-going development of this community resource (https://doi.org/10.1093/jamia/ocaa196).

References

1 Zeng G, Zhou Y. Pharmacotherapy and pulmonary fibrosis risk after SARS-CoV-2 infection. *Lancet Reg Health Am*. 2023;26:100590. https://doi.org/10.1016/j.lana.2023.100590.

2 Adegunsoye A, Baccile R, Best TJ, et al. Pharmacotherapy and pulmonary fibrosis risk after SARS-CoV-2 infection: a prospective nationwide cohort study in the United States. *Lancet Reg Health Am*. 2023;25:100566. https://doi.org/10.1016/j.lana.2023.100566.

3 Johannson KA, Chaudhuri N, Adegunsoye A, Wolters PJ. Treatment of fibrotic interstitial lung disease: current approaches and future directions. *Lancet*. 2021;398(10309):1450–1460.

4 Raghu G, Remy-Jardin M, Richeldi L, et al. Idiopathic pulmonary fibrosis (an update) and progressive pulmonary fibrosis in adults: an official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med*. 2022;205(9):e18–e47. https://doi.org/10.1164/rccm.202202-0399ST.

5 Pugashetti JV, Adegunsoye A, Wu Z, et al. Validation of proposed criteria for progressive pulmonary fibrosis. *Am J Respir Crit Care Med*. 2023;207(1):69–76.