

## A glimpse into long COVID and symptoms

### Authors' reply

In our study, we described the dynamics of long COVID symptoms in COVID-19 survivors with various disease severities, which was one of our main research objectives.<sup>1</sup> In their Correspondence, Chengliang Yang and colleagues noted that delineating individual symptom manifestations at pre-infection and post-infection timepoints is important because some physical symptoms might have been present before SARS-CoV-2 infection. We agree with Yang and colleagues on this matter, and their suggestion that this information could help to find excess symptom burden post-SARS-CoV-2 infection. In our study, to address the problem that some symptoms might have been present before COVID-19, sequelae symptoms were defined as those that were newly occurring and persistent, or worse than the status before getting COVID-19, and could not be explained by an alternative disease.

The sequelae symptoms observed in our study, including the physical symptoms mentioned by Yang and colleagues, might not be specific to SARS-CoV-2 infection, which was acknowledged as a limitation in our published Article.<sup>1</sup> It is not only quite challenging to distinguish whether the observed physical symptoms were direct effects of COVID-19 or not, but also the degree of impairment related to these symptoms. To the best of our knowledge, no validated symptom questionnaire was available at the time of our study. There are also several limitations of self-reported symptom surveys, including information bias and difficulty of objective diagnosis of subjective symptoms (eg, chest pain and palpitations). We mentioned the potential information bias of using self-report symptom questionnaires in our Article.<sup>1</sup>

We did laboratory tests at three follow-up visits, including complete blood count, renal function, liver

function, lipid test, and routine urine. The laboratory findings of 1164 COVID-19 survivors who completed 6-month and 12-month follow-up visits were shown in the appendix (table S5) of our previously published Article.<sup>2</sup> Most survivors showed normal ranges for the laboratory indicators. Due to data insufficiency before COVID-19, it was difficult to interpret the observed laboratory abnormalities among some participants at follow-up because some results might have been new or persistent; thus, we did not show laboratory findings in our 2-year follow-up study. As for SARS-CoV-2 vaccination, of the 1294 COVID-19 survivors who participated in face-to-face interviews at the 2-year follow-up, 1054 (81.5%) were vaccinated, and 705 (54.5%) received at least two doses. The 2-year follow-up was completed on Jan 10, 2022, which, to our knowledge, predated the emergence of the first case of COVID-19 caused by omicron (B.1.1.529) in Wuhan. We cannot provide reinfection information of omicron with data already obtained, but we hope to answer related questions in a future follow-up study.

Specific abnormalities after mild SARS-CoV-2 infection could be helpful to uncover the pathogenesis of long COVID, including brain damage,<sup>3</sup> increased risk of cardiovascular event,<sup>4</sup> or diabetes.<sup>5</sup> There are several hypotheses related to the pathogenesis of long COVID, including persistent virus or viral antigens and RNA in tissues that drive chronic inflammation, the triggering of autoimmunity after acute viral infection, dysbiosis of the microbiome or virome, and unrepaired tissue damage.<sup>6</sup> There is still a long way to go to fully understand the pathogenesis of COVID-19; and once more knowledge is accumulated, this new evidence might also apply to the study of inflammatory processes that are involved in other respiratory infections.

Author declarations remain the same as in the original Article.

Lixue Huang, Xiaoying Gu, Hui Zhang, \*Bin Cao

caobin\_ben@163.com

Department of Pulmonary and Critical Care Medicine, Capital Medical University, Beijing, China (LH, HZ); Department of Pulmonary and Critical Care Medicine, National Center for Respiratory Medicine, Center of Respiratory Medicine, National Clinical Research Center for Respiratory Diseases, China-Japan Friendship Hospital, Beijing, China (LH, XG, HZ, BC); Institute of Clinical Medical Sciences, China-Japan Friendship Hospital, Beijing, China (XG, BC); Institute of Respiratory Medicine, Chinese Academy of Medical Sciences, Beijing, China (BC); Tsinghua University-Peking University Joint Center for Life Sciences, Beijing, China (BC)

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*Lancet Respir Med* 2022

Published Online

June 10, 2022

[https://doi.org/10.1016/S2213-2600\(22\)00126-0](https://doi.org/10.1016/S2213-2600(22)00126-0)



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