

depression should have been handled as either major contributing factors or covariates with confounding effects.

Finally, aside from the depression and anxiety symptoms, other notable and common mental health problems in COVID-19 survivors such as post-traumatic stress disorder symptoms and stigma^{5,6} were not examined. Such problems could lead to a host of negative health outcomes, including depression and anxiety in the survivors of serious infectious diseases.^{7,8}

We declare no competing interests. Y-JZ and WB contributed equally.

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- Huang L, Yao Q, Gu X, et al. 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. *Lancet* 2021; **398**: 747–58.
- Wang H-M, Patrick DL, Edwards TC, Skalicky AM, Zeng HY, Gu WW. Validation of the EQ-5D in a general population sample in urban China. *Qual Life Res* 2012; **21**: 155–60.
- Ryder AG, Yang J, Zhu X, et al. The cultural shaping of depression: somatic symptoms in China, psychological symptoms in North America? *J Abnorm Psychol* 2008; **117**: 300–13.
- Kleinman A. Culture and depression. *N Engl J Med* 2004; **351**: 951–53.
- Yuan Y, Liu Z-H, Zhao Y-J, et al. Prevalence of post-traumatic stress symptoms and its associations with quality of life, demographic and clinical characteristics in COVID-19 survivors during the post-COVID-19 era. *Front Psychiatry* 2021; **12**: 665507.
- Duan W, Bu H, Chen Z. COVID-19-related stigma profiles and risk factors among people who are at high risk of contagion. *Soc Sci Med* 2020; **266**: 113425.
- Park HY, Park WB, Lee SH, et al. Posttraumatic stress disorder and depression of survivors 12 months after the outbreak of Middle East respiratory syndrome in South Korea. *BMC Public Health* 2020; **20**: 605.
- Grov C, Golub SA, Parsons JT, Brennan M, Karpiak SE. Loneliness and HIV-related stigma explain depression among older HIV-positive adults. *AIDS Care* 2010; **22**: 630–39.

The conditions that linger after recovery from COVID-19 are commonly referred to as the long-term effects of COVID-19 (long COVID). The risk for sequelae varies according to the severity of the initial acute SARS-CoV-2 infection.¹

We note that the proportion of patients admitted to intensive care units included in Lixue Huang and colleagues' analysis of 1-year outcomes in hospital survivors with COVID-19 was small (4%) and might not realistically capture the repercussions of long COVID. Furthermore, patients with comorbid activity-limiting health conditions or disabilities, a patient demographic previously shown to have an increased prevalence of long COVID by the UK Office for National Statistics, were excluded.³

Anxiety or depression were observed infrequently in patients at both 6 months (23%) and 12 months (26%). Self-reported symptoms of depression might be misleading and overestimate the actual prevalence. This overestimation might explain why only one patient with COVID-19 reported participation in a psychological intervention programme.² In the future, the investigators might consider using questionnaires specific to depression and anxiety to avoid this issue.

Cytokines are closely associated with the progression and severity of chronic fatigue syndrome.⁴ Given the high rate of fatigue and weakness and the availability of data on cytokines, are the investigators able to compare the difference in the number of survivors between patients with fatigue or muscle weakness and those without fatigue or muscle weakness?

Lastly, reinfection with SARS-CoV-2 variants have been confirmed with genetic evidence.⁵ It is unclear whether patients with long COVID also have an increased susceptibility to reinfection because of the poor durability of their antibody response. Despite the success of COVID-19 vaccines, their effectiveness in preventing long COVID has yet to be elucidated.

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- Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. *Nature* 2021; **594**: 259–64.
- Huang L, Yao Q, Gu X, et al. 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. *Lancet* 2021; **398**: 747–58.
- The UK Office for National Statistics. Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK: 1 July 2021. July 1, 2021. <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/prevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk/1july2021> (accessed Aug 29, 2021).
- Yang T, Yang Y, Wang D, et al. The clinical value of cytokines in chronic fatigue syndrome. *J Transl Med* 2019; **17**: 213.
- To KK-W, Hung IF-N, Ip JD, et al. COVID-19 re-infection by a phylogenetically distinct SARS-coronavirus-2 strain confirmed by whole genome sequencing. *Clin Infect Dis* 2020; published online Aug 25. <https://doi.org/10.1093/cid/ciaa1275>.

Authors' reply

Yan-Jie Zhao and colleagues and Chengliang Yang and colleagues all recommend specific questionnaires to evaluate depression and anxiety symptoms in hospital survivors with COVID-19 1 year after onset.¹ We agree that the professional questionnaires could provide the actual prevalence of psychiatric symptoms. However, these questionnaires are somewhat complex and time-consuming. It is challenging to integrate all these assessments into our follow-up study.¹ The EuroQol five-dimension five-level (EQ-5D-5L) questionnaire is commonly used to assess the quality of life from five domains in clinical studies. The EQ-5D-5L questionnaire used in our research is from the Chinese version of the EQ-5D user guide.² Zhao and colleagues point out that the EQ-5D-5L

item on anxiety or depression was not validated in Chinese populations. However, to our knowledge, the reliability of the Chinese EQ-5D has been validated in China, and it has shown acceptable construct validity and fair-to-moderate levels of test-retest reliability.³ Additionally, according to a large multinational study involving China, the EQ-5D-5L provided precise measurement at individual and group levels compared with the EQ-5D three-level, both in terms of descriptive system data and usefulness.⁴ Hence, we believe that descriptive system data from the EQ-5D-5L questionnaire could well reflect the health status of our cohort.

We acknowledged that the low proportion of patients admitted to the intensive care unit in our cohort limits the generalisability of the study findings. Similarly, the findings cannot be generalised to those who were excluded from the study.

We appreciate Yang and colleagues' interest in the association between cytokines and fatigue syndrome. As shown in the appendix of the Article,¹ no statistically significant association between cytokine change (at discharge until 6 months) and fatigue or muscle weakness was apparent. However, because of the small number of patients with cytokine tests, these findings should be interpreted as exploratory and need to be validated in a larger sample population.

Zhao and colleagues are concerned that all the somatic symptoms at follow-up could be attributed to depression or anxiety or both, rather than the so-called sequelae symptoms caused by COVID-19. We agree these sequelae symptoms might not be directly caused by COVID-19, a factor that is difficult to differentiate. The definition of sequelae symptoms in our study is consistent with the current concept of long COVID,⁵ whether directly caused by COVID-19 or partly attributed to depression or anxiety, so it is appropriate to call it COVID-19-related sequelae symptoms.

We appreciate Zhao and colleagues' suggestion to explore the post-traumatic stress disorder symptoms and stigma of patients recovered from COVID-19 in the future. In addition, Yang and colleagues pointed out that it is unclear whether patients with long COVID have an increased susceptibility to reinfection and whether COVID-19 vaccines could play a role in preventing long COVID. Answering these research questions will require the full breadth of scientific and high-quality clinical studies. The scientific and medical communities might wish to collaborate to explore the mechanism and pathogenesis of long COVID.

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- Huang L, Yao Q, Gu X, et al. 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. *Lancet* 2021; **398**: 747–58.
- EuroQol Research Foundation. EQ-5D-5L user guide, version 3.0. 2019. <https://euroqol.org/wp-content/uploads/2021/01/EQ-5D-5LUserguide-08-0421.pdf> (accessed May 26, 2020).
- Wang H-M, Patrick DL, Edwards TC, Skalicky AM, Zeng H-Y, Gu W-W. Validation of the EQ-5D in a general population sample in urban China. *Qual Life Res* 2012; **21**: 155–60.
- Janssen MF, Bonsel GJ, Luo N. Is EQ-5D-5L better than EQ-5D-3L? A head-to-head comparison of descriptive systems and value sets from seven countries. *Pharmacoeconomics* 2018; **36**: 675–97.
- Nalbandian A, Sehgal K, Gupta A, et al. Post-acute COVID-19 syndrome. *Nat Med* 2021; **27**: 601–15.

CoronaVac efficacy data from Turkey

Mine Tanriover and colleagues¹ report that the efficacy of CoronaVac against laboratory-confirmed symptomatic COVID-19 in a trial in Turkey is 83.5% (95% CI 65.4–92.1). By contrast, the efficacy of CoronaVac against symptomatic COVID-19 has been estimated at 50.7% (36.0–62.0) in a Brazilian trial and at 65.3% (20.0–85.1) in an Indonesian trial.^{2,3} Noting that post-vaccination neutralising antibody titres are quite strongly associated with vaccine efficacy against symptomatic infection,^{4,5} the efficacy estimated from the Turkish dataset is much higher than we would expect given the modest post-vaccination neutralising antibody titres after the second dose of CoronaVac.

There was a high proportion of hospitalised COVID-19 cases in the placebo group, accounting for six (19%) of the 32 cases included in the interim analysis,¹ compared with 6% and 0% of cases in the Brazilian and Indonesian trials, respectively.^{2,3} It is possible that some milder cases were missed in this trial, and the efficacy could therefore be skewed towards a higher value given that CoronaVac, similar to other COVID-19 vaccines, has a higher efficacy against severe disease than mild disease. Moreover, the short median follow-up time of 15 days (IQR 8–20) at risk could reduce the generalisability of the findings.

Given the global shortage of vaccines, the approval and distribution of as many effective vaccines as possible will maximise the number of lives saved during the COVID-19 pandemic. However, reports of a high efficacy in clinical trials that are not borne out by real-world vaccine effectiveness data would damage confidence in vaccines.

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