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Letter to the Editor

The effect of molnupiravir on post-acute outcome of COVID-19 survivors

Dear Editor,

We read with great interest the review article by Gary et al., in which they raised several concerns about the use of molnupiravir in the treatment of patients with COVID-19.\(^1\) At the end of 2021, molnupiravir obtained emergency use authorization from the United States Food and Drug Administration and was recommended for non-hospitalized patients with mild-to-moderate COVID-19 at high risk of progression to severe disease.\(^1\)\(^2\) This recommendation was based on the findings of the MOVe-OUT clinical trial, in which early treatment with molnupiravir would lower the risk of hospitalization or death on day 29 among adult patients at high risk of severe COVID-19. In addition, compared to patients receiving placebo, its post hoc analysis showed that patients receiving molnupiravir were not only associated with a faster normalization of C-reactive protein level and peripheral oxygen saturation but also a decreased demand for respiratory intervention.\(^3\) These findings indicated the short-term beneficial effects of molnupiravir in selected patients with COVID-19; however, the long-term effect of molnupiravir was unknown. Therefore, this retrospective cohort study was conducted to evaluate the impact of molnupiravir on COVID-19 survivors during the post-acute phase of the infection.

This study used the data from the TriNetX Research Network, which provides real-time information on more than 250 million patients from 120 Healthcare Organizations (HCOs). As previously described,\(^4\)\(^5\) we identified adult patients who tested positive for SARS-CoV-2 infection or were diagnosed with COVID-19 from March 1, 2020 to June 30, 2022 from the platform on February 16, 2023. To assess the post-acute outcomes, we excluded the patients who died within the first month of COVID-19. To avoid the confounding effect of other potential effective treatments for patients with mild-to-moderate COVID-19, we also excluded those who have ever received nirmatrelvir plus ritonavir, remdesivir, monoclonal antibodies, or convalescent plasma for acute COVID-19. Subsequently, we divided these candidates into two groups according to the use of molnupiravir. Patients who received molnupiravir were assigned to the study group, and those who did not receive any anti-viral agents were to the control group. To adjust for the baseline characteristics between the study and the control group, propensity score method with a 1:1 matching by age, gender, race, ethnicity, and comorbid medical conditions was used to form two matched groups.

The primary outcome was the composite endpoint of all-cause hospitalization or death from 30 to 180 days after the diagnosis of COVID-19. The secondary outcomes included all-cause hospitalizations and mortality separately during the follow-up period. All the comparisons of the post-acute outcomes between groups were calculated using the hazard ratio (HR) with 95% confidence interval (95% CI) by the built-in statistical function of the TriNetX network.

This study included a total of 2,414,918 patients with COVID-19, consisting of 3600 patients who received molnupiravir (study group) and 2,411,318 patients who did not receive molnupiravir (control group) (Fig. 1). Compared with the control group, the study group had a higher average age (61.4 ± 15.8 versus 46.1 ± 18.0). In addition, the study group consisted of predominantly white and non-Hispanic or Latino. Moreover, the study group had a higher body mass index and more comorbidities, including hypertension, type 2 diabetes mellitus, chronic lower respiratory diseases, nicotine dependence, heart disease, chronic kidney disease, liver disease, and neoplasms than the control group. After propensity score matching, 3600 matched cases were retained in each group (Table 1).

During the follow-up period of 30–180 days, 128 patients in the study group and 227 patients in the control group reached the composite endpoint of all-cause hospitalization or mortality. The study group had a lower hazard ratio (HR) of 0.582 (95% confidence interval [CI]: 0.469, 0.723) and a lower probability of all-cause hospitalization or mortality when compared to the control group (log-rank test, p < 0.0001) (Fig. 2). Considering all-cause hospitalization and mortality separately, the study group also exhibited the beneficial impacts of molnupiravir on reducing both all-cause hospitalization or mortality (HR, 0.616; 95% CI, 0.490, 0.775) and all-cause mortality (HR 0.494; 95% CI, 0.304, 0.802). Figs. 3(a) and 3(b) demonstrated that treatment with molnupiravir had lower probabilities of all-cause hospitalization (log-rank test, p < 0.0001) and all-cause mortality (log-rank test, p = 0.0036) correspondingly (Table 2).

The final outcome analysis was performed using the 7200 patients, with 3600 patients in each cohort, and found that molnupiravir could reduce post-acute all-cause hospitalization or mortality among COVID-19 survivors. This finding was consistent with a previous study, in which patients receiving nirmatrelvir plus ritonavir could have a lower risk of all-cause hospitalization or mortality (HR, 0.543; 95% CI, 0.495–0.597) 30–180 days after a documented COVID-19 diagnosis.\(^6\) Both findings indicated that the novel oral anti-viral agents, including molnupiravir and nirmatrelvir plus ritonavir, are able to provide further clinical benefits for COVID-19 survivors.

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survivors during the post-acute phase. These findings suggested the promising effects of antivirals in the prevention of post-acute COVID-19 complications.

The association between molnupiravir and the post-acute outcome of patients with COVID-19 in this study could be explained by the following reasons. A significant portion of patients surviving acute COVID-19 would experience the post-acute sequelae of COVID-19 or long COVID, which was caused by SARS-CoV-2 direct injury or its associated immune/inflammatory response. Early antiviral treatment may help facilitate the virological eradication and reduce further inflammatory or immunologic response. Therefore, antiviral therapies could potentially reduce the risk of post-acute complications after SARS-CoV-2 infection.

The use of the TriNetX Research Network enabled our study to recruit cohort members from a large population-based database of over 120 HCOs and the built-in propensity score matching was used.
to reduce confounding variables despite the retrospective nature of the database. However, our findings should be interpreted in light of the following limitations. First, our acquired data may be subjected to residual confounding variables such as vaccination status, COVID-19 severity, SARS-CoV-2 variants, and the use of other anti-COVID-19 treatments that were not listed in the cohort construction, particularly for corticosteroids and interleukin-6 blockade agents. Second, as with all coding-based studies, our results are susceptible to misdiagnosis, inaccurate coding, and errors in documentation. Hence, further study is warranted to clarify these issues.

In conclusion, in addition to the clinical benefit of molnupiravir for acute COVID-19, 1,2 our study demonstrated the extended effect of molnupiravir in reducing the risks of all-cause hospitalization and mortality in the post-acute phase following SARS-CoV-2 infection.

### Table 1
Comparison of characteristics of patients receiving and not receiving molnupiravir before and after propensity score matching.

| Table 1                                      | Before matching                          | After matching                           | p-value  |
|----------------------------------------------|------------------------------------------|------------------------------------------|----------|
| Age at index (mean ± SD)                     | Molnupiravir group (n = 3600)            | Control group (n = 2,411,318)            | Standard difference | Molnupiravir group (n = 3600) | Control group (n = 2,411,318) | Standard difference |
| Gender (%)                                   | Male: 1503 (41.8)                        | Female: 2097 (58.3)                      | 0.009    | Male: 1503 (41.8)                        | Female: 2097 (58.3)                      | 0.009    |
| Race (%)                                     | White: 3184 (88.4)                       | Black or African American: 230 (6.4)     | 0.854    | White: 3184 (88.4)                       | Black or African American: 230 (6.4)     | 0.854    |
| Ethnicity (%)                                | Not Hispanic or Latino: 3209 (89.1)      | Hispanic or Latino: 140 (3.9)            | 1.186    | Not Hispanic or Latino: 3209 (89.1)      | Hispanic or Latino: 140 (3.9)            | 1.186    |
| Body mass index, kg/m^2 (mean ± SD)         | 30.8 ± 7.0                               | 25–30 kg/m^2                             | 0.146    | 30.8 ± 7.0                               | 25–30 kg/m^2                             | 0.146    |
| Comorbidities (%)                            | Hypertension: 2010 (55.8)                | Type 2 diabetes mellitus: 962 (26.7)     | 0.871    | Hypertension: 2010 (55.8)                | Type 2 diabetes mellitus: 962 (26.7)     | 0.871    |
| Chronic lower respiratory diseases           | Asthma: 757 (21)                         | Chronic obstructive pulmonary disease    | 0.266    | Asthma: 757 (21)                         | Chronic obstructive pulmonary disease    | 0.266    |
| Bronchitis                                   | Emphysema: 61 (1.7)                      | Bronchiectasis                           | 0.092    | Emphysema: 61 (1.7)                      | Bronchiectasis                           | 0.092    |
| Simple and mucopurulent chronic bronchitis   | Lung function: 350 (9.7)                 | Unspecified chronic bronchitis           | 0.181    | Lung function: 350 (9.7)                 | Unspecified chronic bronchitis           | 0.181    |
| Ischemic heart diseases                      | Other forms of heart disease             | Chronic kidney disease, stage 4           | 0.499    | Other forms of heart disease             | Chronic kidney disease, stage 4           | 0.499    |
| Chronic kidney disease, stage 3              | Diseases of liver                        | Fatty liver                              | 0.291    | Chronic kidney disease, stage 3           | Diseases of liver                        | 0.291    |

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1. W.-H. Hsu, B.-W. Shiau, Y.-W. Tsai et al. Journal of Infection xxx (xxxx) xxx–xxx
Declaration of Competing Interest

All authors declared that there was no conflict of interest.

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