Nirmatrelvir-ritonavir treatment on SARS-CoV-2 viral dynamics in high altitude habitants

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Social and environmental factors of high-altitude regions such as the Tibet plateau are proposed to protect habitants against SARS-CoV-2 infection.[1,2] However, once infected, high altitude habitants may suffer more severe respiratory stress due to the compounding effect of hypobaric hypoxia and SARS-CoV-2-induced hypoxemia.[2] Access to comprehensive medical care and therapeutic options are often limited in high-altitude regions, making orally available antivirals such as nirmatrelvir-ritonavir essential for high altitude habitants with COVID-19.[3]

Nirmatrelvir-ritonavir reduces viral load by inhibiting the main protease of SARS-CoV-2, which effectively prevents assembly of new virions.[4] A caveat of this strategy is the requirement of early treatment, normally within 5 days after symptom onset, which is challenging in high-altitude regions with limited testing and drug distribution capacities. Chronic hypoxia may also alter the infection pattern of SARS-CoV-2 by reducing ACE2 expression in lung epithelial cells, which could render nirmatrelvir-ritonavir less effective in high altitude habitants.[5]

Here, we analyzed a cohort of 314 hospitalized COVID-19 cases in Nyingchi city of the Tibet Autonomous Region of China (alt. 3100 m), who were infected by the omicron BA.2.76 subvariant (appendix p 2). In-hospital procedures including viral testing, symptom monitoring, and treatments were detailed in the Methods (appendix p 7–9). Most cases had mild or no symptoms, and all cases survived the infection. Boost vaccination status was not associated with peak viral load or viral clearance likely due to wanning immunity and high immune evasiveness of omicron (appendix p 3).

89 cases with indications were prescribed nirmatrelvir-ritonavir at a median of 2 (IQR 1–2) days after viral positive. Despite of worse demographic and clinical characteristics (appendix p 9), viral loads in upper respiratory tracts decreased faster among nirmatrelvir-ritonavir recipients with geometric mean dropped below detection threshold 1 day earlier than control group (Fig. 1A). Proportions of viral clearance at day 10 since viral positive were 62.9% and 36.4% (odds ratio 2.96, 95% CI 1.75–4.83) in nirmatrelvir-ritonavir and control groups, respectively (Fig. 1B). Cox regression for time to viral clearance estimated the hazard ratio of nirmatrelvir-ritonavir vs control as 2.43 (95% CI 1.83–3.23) after adjusting for confounders (Fig. 1C). Of note, viral rebound was observed in 10.1% and 9.8% patients in nirmatrelvir-ritonavir and control groups, respectively.

Stratification by high-altitude habitant status or ethnicity showed comparable association of nirmatrelvir-ritonavir with early viral clearance in every group (appendix p 4–5), indicating that neither physiological nor genetic adaptation to high-altitude environment might interfere with therapeutic mechanisms of nirmatrelvir-ritonavir. In contrast, the adjusted hazard ratio of nirmatrelvir-ritonavir for viral clearance was higher among male subjects (3.16 vs 1.93 of females), indicating potential sex-associated mechanism regulating the therapeutic efficacy of nirmatrelvir-ritonavir (appendix p 6–7). Booster vaccination was also associated with higher adjusted hazard ratio of nirmatrelvir-ritonavir for viral clearance (3.50 vs 1.87 of subjects not booster vaccinated), supporting a possible synergy or mutual dependence between nirmatrelvir-ritonavir and

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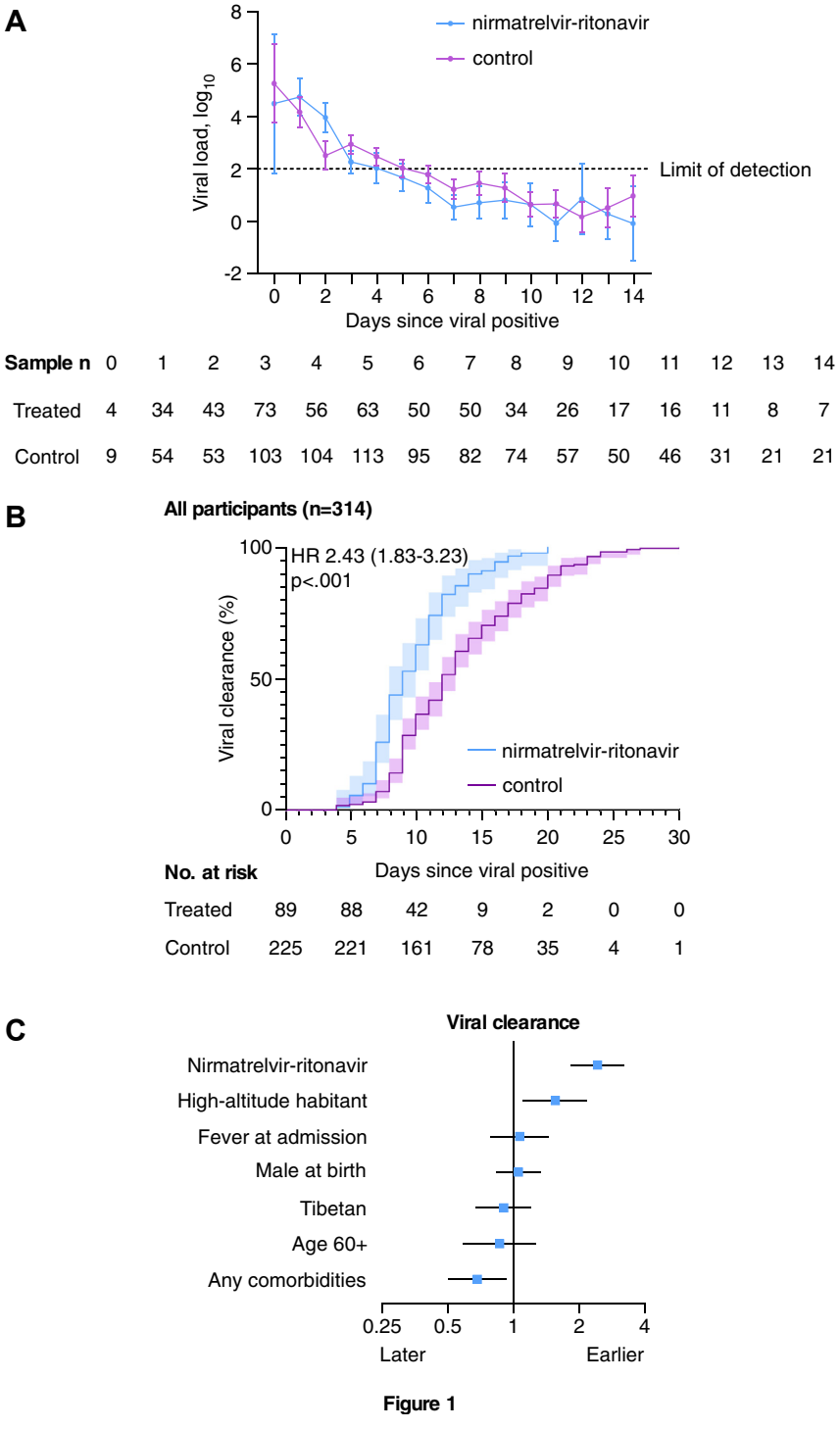

Figure 1

Fig. 1: **Nirmatrelvir-ritonavir treatment on SARS-CoV-2 viral dynamics in the upper respiratory tract.** (**A**) Viral load dynamics in upper respiratory tracts of SARS-CoV-2 infected individuals treated with or without nirmatrelvir-ritonavir. Time zero corresponds to the time at which a patient first tested positive for SARS-CoV-2 infection. Dots and error bars represent geometric means and 95% confidence intervals (CI). Horizontal dashed line indicates the limit of detection of qRT-PCR assay (100 copies/ml). Sample number at each data point is listed below the plot. (**B**) Cumulative event plots of time-to-viral clearance according to nirmatrelvir-ritonavir treatment status. Hazard ratios (HR) and CI were estimated by Cox proportional hazard model after adjusting for confounders listed in panel C. (**C**) Forest plots showing Cox proportional hazard model analysis of indicated factors with time-to-viral clearance as the dependent variable (n = 314). Adjusted HR of each factor is expressed on log axis. Squares and error bars represented HR and 95% CI. Directional trends were labeled under the X axis.

vaccine-elicited immunity (appendix p 6–7), which might be unique in high-altitude settings.[6] Among subjects with comorbidities, nirmatrelvir-ritonavir was associated with 50% (9/18 days), 61% (12.5/20.5), and 33% (5/15) reduction of median viral positive duration in all subjects and hypertension or diabetes subgroups, respectively (appendix p 8). However, some of these stratified analyses had insufficient statistical power due to limited sample sizes and results should be interpreted with caution.

Our data provided preliminary evidence that nirmatrelvir-ritonavir remained effective in accelerating omicron viral clearance at high-altitude settings, and highlighted the importance of nirmatrelvir-ritonavir availability and timely prescription in regions with limited medical resources. Nonetheless, further studies are needed to assess the protective effect of nirmatrelvir-ritonavir against severe COVID-19 in high-altitude regions.

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Contributors
AL and XZ contributed equally. AL, XZ, and XR abstracted case information and did clinical investigations; LT did statistical analysis; DH and YZ interpreted clinical findings; PH conceived the study, analyzed data, and wrote the manuscript. No authors were precluded from accessing data in the study, and they accept responsibility to submit for publication. All authors read and approve the final manuscript.

Declaration of interests
The authors declare no competing interests.

Appendix A. Supplementary data
Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2022.100671.

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