# Evaluate clinical effectiveness of Azvudine with data rather than speculation

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June 19, 2023

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To the Editor,

We appreciate the interest in our article entitled "Real-world effectiveness of Azvudine versus nirmatrelvir-ritonavir in hospitalized patients with COVID-19: A retrospective cohort study".

In their study, Ma et al. stated that antiviral therapies must be administered within five days of symptom onset to be effective. However, our study population included approximately 90% of patients beyond this treatment window. Moreover, we were unable to provide virological results, leading to Ma et al.'s speculation that treatment was unlikely to benefit patients in our study. They further praised the benefits of nirmatrelvir-ritonavir in COVID-19 patients and demonstrated their results supporting a faster time to nucleic acid negative conversion compared to patients receiving Azvudine. In a phase III trial, patients treated with Azvudine only showed a 50% reduction in viral load on the fifth day of treatment, making it difficult to achieve significant clinical efficacy. Ma et al. also concluded that the dose of Azvudine was insufficient for its antiviral effects, using data from drug experimental and pharmacokinetic studies. Finally, they called for the time to make more effective drugs available to COVID-19 patients.[1]

As a retrospective study, we sought to collect more information, particularly on cycle thresholds in COVID-19 patients. However, as we previously reported, the cycle threshold value was no longer used as a discharge criterion during the period and was not regularly checked.[2] Moreover, most electronic health records of

COVID-19 patients only recorded quantitative results (positive or negative) upon admission, hence virological data was lacking. Nevertheless, it was not necessary for our study, which aimed to evaluate the real-world clinical effectiveness (composite outcomes and mortality). [3]

Azvudine and nirmatrelvir-ritonavir were recommended for the treatment of COVID-19 patients as early as possible, but these drugs were not strictly used according to the instructions during the special period. We acknowledged several limitations in our retrospective study, including the possibility of selection bias and confounding by indication. We also emphasized that our conclusions were solely based on data from our hospital and that the generalization of our findings required more high-quality and multi-center clinical trials.[3] As clinicians, with limited knowledge about drug experimental and pharmacokinetics studies, we refrain from making any response on the topic of its antiviral effect. If there are any questions concerning the antiviral effect, we suggest contacting the corresponding authors of these studies.[4,5] We can, however, discuss the clinical effectiveness of the drugs.

We agree that numerous studies from other countries support the benefits of nirmatrelvir-ritonavir in treating COVID-19 patients.[6] However, a multi-center randomized controlled study based on Chinese patients failed to detect a significant reduction in the risk of all-cause mortality on day 28 and the duration of virus clearance in severe adult COVID-19 patients.[7] As our study mainly included severe COVID-19 patients in China, the limited efficacy of nirmatrelvir-ritonavir is not surprising.[3,8] While Ma et al. found a faster time to nucleic acid negative conversion in patients receiving nirmatrelvir-ritonavir compared to those receiving Azvudine,[1] it did not entirely negate our findings that support the better clinical benefit of Azvudine.[3]Evaluating a drug's effectiveness requires clinical data, rather than piecing together several basic articles to make a speculation solely based on its antiviral effect. For instance, remdesivir can effectively inhibit COVID-19 infection in vitro but has no significant effect on COVID-19 patients who are already being ventilated.[9]Similarly, metformin, the most commonly used oral type 2 diabetic drug, functions in many diseases, including avoiding long COVID.[10] Nowadays, compared with other anti-COVID-19 drugs, there is limited clinical study on Azvudine. Therefore, we call for more real-world studies to evaluate the effectiveness of Azvudine in COVID-19 patients.

Finally, we appreciate the feedback from some readers regarding the flowchart of patient screening in Figure 1. To avoid any confusion, we would like to clarify that patients were repeatedly counted if they met individual exclusion criteria in the study. Additionally, pregnant patients were mistakenly classified to patients with history diseases. After matching, none of pregnant patients were included in Azudine and nirmatrelvir-ritonavir group. Therefore, our conclusions were still consistent.

**Declaration of Competing Interest:** None.

**Acknowledgement:** This work was supported by the National Natural Science Foundation of China (Grant Nos. 82102803, 82272849 to G. D.), National Natural Science Foundation of Hunan Province (Grant Nos. 2021JJ40976 to G. D.) and Natural Science Fund for Outstanding Youths in Hunan Province (2023JJ20093 to G.D.).

**Role of the funding source:** The funding sources had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the article for publication. All the authors had full access to all the data in the study and agree to submit the manuscript for publication.

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