

Delayed treatment with nirmatrelvir/ritonavir could remain effective in patients with Omicron BA.2.2 variant of COVID-19

Dear Editor,

In late February 2022, the Omicron BA.2.2 subvariant drove the outbreak of COVID-19 and rapidly spread through many parts of the world. Omicron-infected individuals aged ≥ 80 years who are unvaccinated are particularly at high risk of poor outcomes.

COVID-19 vaccines and antiviral therapeutics have protected individuals most at risk from the disease.¹ Paxlovid (Pfizer, New York, NY, US), composed of nirmatrelvir and ritonavir, is an orally bioavailable SARS-CoV-2 protease inhibitor.² Nirmatrelvir, a SARS-CoV-2 main protease (M^{pro}) inhibitor (i.e. 3CL protease inhibitor), decreases viral replication in the early stages of the disease to prevent progression to severe COVID-19. Ritonavir is co-administered with nirmatrelvir to slow its metabolism, so that nirmatrelvir can remain active in the body at higher concentrations for a longer time, to combat the virus.

The EPIC-HR trial and real-world studies have reported that treatment with Paxlovid within the first 5 days of SARS-CoV-2 infection can effectively reduce the mortality or hospitalisation rate of patients.³⁻⁵ This has been observed in various populations, including children aged 6–14 years, adults aged ≥ 60 years, and patients who are immunocompromised.⁶⁻⁸ However, evidence for Paxlovid has been based on its effects in patients treated within 5 days after diagnosis. The manufacturer's instructions also recommend the drug administration to be initiated within 5 days of symptom onset.⁹ However, the rapid surge of COVID-19 cases during the pandemic resulted in major difficulties for timely therapy. Our study aimed to assess the effectiveness of Paxlovid in patients with disease onset duration of ≤ 5 days as well as > 5 days. We also observed the effectiveness of Paxlovid treatment for oldest-old patients (aged ≥ 85 years) and patients with malignant solid tumours who were infected with Omicron variant of COVID-19.

This was a retrospective observational study of patients hospitalised. COVID-19 was diagnosed using real-time reverse transcription-polymerase chain reaction (RT-PCR). RT-PCR cycle threshold (Ct) values were used as an indirect method for quantifying viral replication. Viral elimination was defined as negative

for both *ORF1ab* and *N* genes (Ct value ≥ 35) on different days. Time to viral elimination was used as an indicator of Paxlovid effectiveness.

From 10 April to 22 June 2022, 113 patients in our hospital received Paxlovid and were included in the study. Their median time from diagnosis to Paxlovid initiation was 5 days (interquartile range [IQR] 3–8). Additionally, 565 patients matched by age, sex and vaccination rate using propensity score matching (1:5 matching), who did not receive Paxlovid, were included as controls (online Supplementary Table S1). Paxlovid recipients had shorter duration of hospitalisation compared to controls (6 days [IQR 5–8] versus 8 days [IQR 5–12], $P < 0.001$) (online Supplementary Table S1). They also had a shorter time from diagnosis to viral elimination (9 days [IQR 7–13] vs 13 days [IQR 10–16], $P < 0.001$) (Fig. 1A).

The median times from admission to Paxlovid initiation in the early treatment group (≤ 5 days after diagnosis) and delayed treatment group (> 5 days after diagnosis) were 2 days [IQR 1–2] and 4 days [IQR 2–6], respectively. The median time from treatment to the day of viral elimination was similar in both groups (4 days [IQR 3–6] vs 3 days [IQR 2–5], $P = 0.529$) (online Supplementary Table S2). The Kaplan-Meier survival curves of the 2 groups were similar when the difference in the Paxlovid initiation time was removed ($P = 0.663$) (Fig. 1B). Likewise, after Paxlovid treatment, clearance of viral load as measured by *ORF1ab* viral gene replication was very similar between the 2 groups (Fig. 1C).

There were 262 oldest-old patients hospitalised with SARS-CoV-2, including 38 (14.5%) who had received a prescription for Paxlovid. The oldest-old Paxlovid recipients had a shorter time from diagnosis to viral elimination than those who did not receive Paxlovid (10 days [IQR 7–14] vs 14 days [IQR 11–18], $P < 0.001$) (online Supplementary Table S3). Among these patients, 21 (55.3%) received Paxlovid treatment > 5 days after diagnosis. No significant differences were found in the median time from Paxlovid treatment to the day of viral elimination between patients treated within and beyond 5 days after diagnosis (4 days [IQR 3–5] vs 4 days [IQR 3–6], $P = 0.964$)

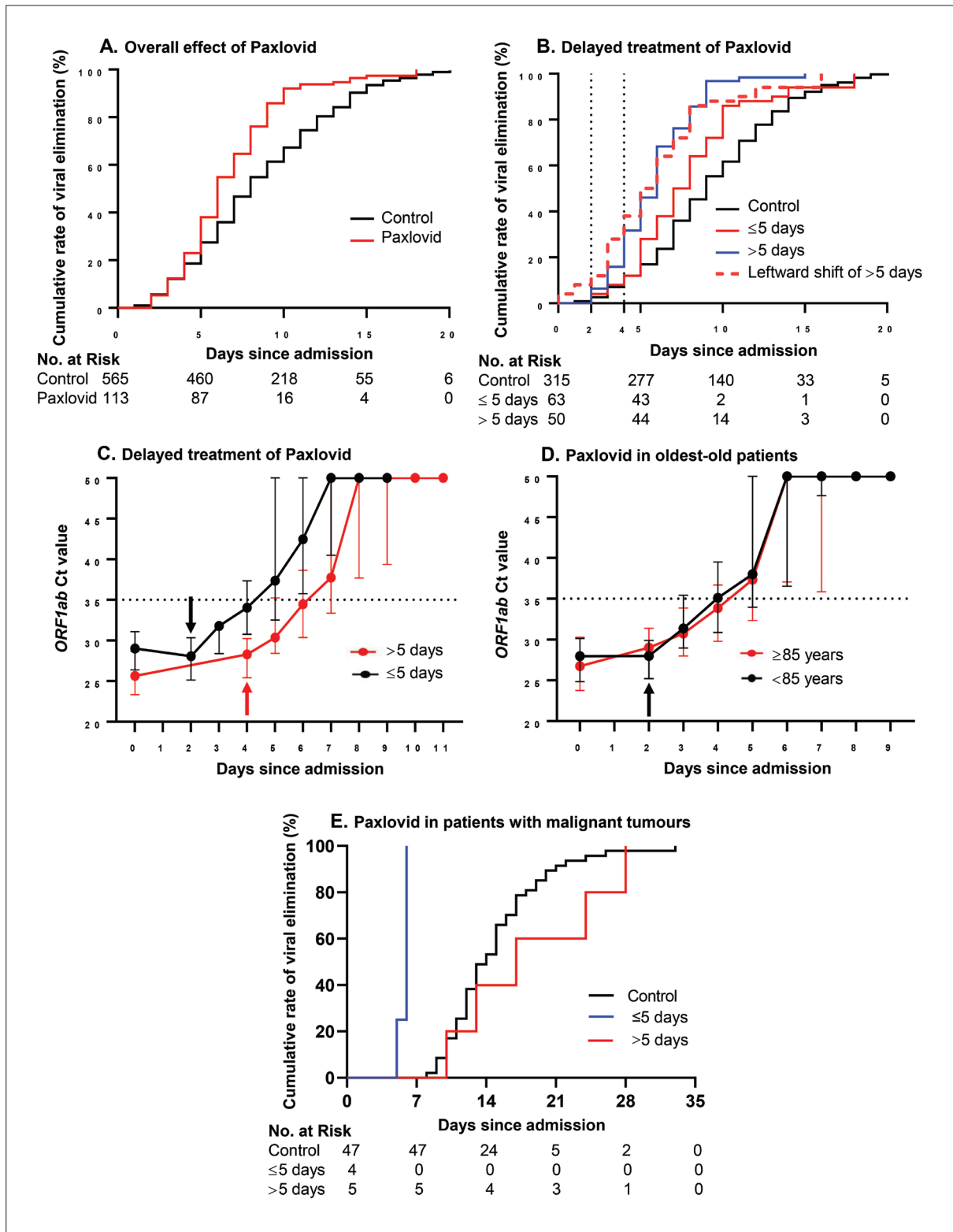


Fig. 1. Clearance of viral load and duration of viral elimination after Paxlovid treatment. (A) The comparison of cumulative rate of viral elimination in Paxlovid-treated patients versus controls who did not receive Paxlovid. (B) The cumulative rate of viral elimination in patients with Paxlovid prescriptions within 5 days vs beyond 5 days since diagnosis. (C) The changes of *ORF1ab* Ct values in patients with Paxlovid prescriptions within or beyond 5 days since diagnosis. Black and red arrows indicate the median time of Paxlovid initiation in 2 groups. (D) The changes of *ORF1ab* Ct values in patients with Paxlovid prescriptions of different age groups. Black arrow indicates the median time of Paxlovid initiation. Data in (C) and (D) are shown as medians and interquartile ranges. (E) The cumulative rate of viral elimination in patients with malignant tumours who received Paxlovid within or beyond 5 days since diagnosis.

(Supplementary Table S4). No difference was observed in the clearance of viral load after Paxlovid treatment between patients aged ≥ 85 years and < 85 years (Fig. 1D).

There were 56 patients with malignant solid tumours in this study, including 9 (16.1%) who had received a prescription for Paxlovid. The viral elimination time of Paxlovid recipients was shorter than the patients who did not receive Paxlovid (10 days [IQR 6–20] vs 14 days [IQR 11–17], $P < 0.001$) (online Supplementary Table S5). However, patients who were given Paxlovid prescription after 5 days of diagnosis had a significantly longer time of viral elimination since Paxlovid initiation (4 days [IQR 3–6] vs 2 days [IQR 1–3], $P = 0.090$) (Fig. 1E and online Supplementary Table S6).

In summary, this study showed that Paxlovid treatment facilitated the eradication of SARS-CoV-2 Omicron variant, with a significantly shortened hospitalisation time. Paxlovid recipients had 4 days less time to viral elimination from diagnosis than the controls who did not receive Paxlovid. Viral load of SARS-CoV-2 decreased rapidly under Paxlovid treatment and became negative within 3 or 4 days, regardless of age and initiation time. Paxlovid effectiveness was similar in patients treated within and beyond 5 days after diagnosis. The same clinical benefit was also observed in oldest-old patients. However, for patients with malignant tumours, Paxlovid is recommended to be initiated as soon as possible after infection, since its early administration is more effective than delayed treatment.

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Wenjie Wang ^{*1MD}, Jing Wan ^{*1MD}, Wei Du ^{1MD},
Jing Song ^{1MD}, Ye Lu ^{1MD}, Shuiming Gu ^{2MD},
Yunhai Feng ^{3MD}, Gang Wang ^{4PhD},
Minfang Tao ^{5,6MD}, Jun Yin ^{1,7MD}

¹ Department of Endocrinology and Metabolism, Shanghai Eighth People's Hospital, Shanghai, China

² Department of Cardiology, Shanghai Eighth People's Hospital, Shanghai, China

³ Department of Otolaryngology, Shanghai Eighth People's Hospital, Shanghai, China

⁴ Department of Pharmacy, Shanghai Eighth People's Hospital, Shanghai, China

⁵ Department of Gynaecology and Obstetrics, Shanghai Eighth People's Hospital, Shanghai, China

⁶ Department of Gynaecology and Obstetrics, Shanghai Jiao Tong University School of Medicine Affiliated Sixth People's Hospital, Shanghai, China

⁷ Department of Endocrinology and Metabolism, Shanghai Jiao Tong University School of Medicine Affiliated Sixth People's Hospital, Shanghai, China

Correspondence: Dr Jun Yin, Department of Endocrinology and Metabolism, Shanghai Eighth People's Hospital, 8 Caobao Road, Shanghai 200235, China.

Email: yinjun@sjtu.edu.cn

Dr Minfang Tao, Department of Obstetrics and Gynecology, Shanghai Eighth People's Hospital, 8 Caobao Road, Shanghai 200235, China.

Email: taomf@126.com

* Joint first authors