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Benefit of Immediate Initiation of Nirmatrelvir/Ritonavir against Long COVID: Real-world Cohort Study

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Introduction

- Nirmatrelvir/ritonavir, an antiviral treatment for COVID-19, is generally recommended to be prescribed within 5 days of diagnosis or symptom onset.
- However, given the typically short duration of acute symptoms, especially for Omicron infections, questions have been raised about the timing of antiviral treatment.
- This study examined the effect of nirmatrelvir/ritonavir at different initiation time against post-COVID conditions using real-world data.

Methods

- This is a retrospective cohort study that utilized real-world inpatient records, vaccination, and confirmed COVID-19 case data in Hong Kong.
- Patients tested positive for SARS-CoV-2 between Mar 16, 2022 and Nov 9, 2023 were included.
- The treatment group included patients prescribed with nirmatrelvir/ritonavir by different number of days after positive RT-PCR test date.
- The primary outcomes are post-acute inpatient death and all-cause hospitalization.
- Standardized-mortality-ratio weighting was applied to balance covariates, and Cox proportional hazards regression was used to examine the associations.

Results

- Among 38,290 included patients, 22,312 received no treatment, and 10,028, 4,973, 597, 211, 82, and 87 initiated nirmatrelvir/ritonavir treatment at day 0, 1, 2, 3, 4, ≥5 after diagnosis, respectively.
- The effect size decreased significantly along with the deferred initiation of nirmatrelvir/ritonavir (Figures 1 and 2).
- Compared to no treatment group, an immediate initiation of nirmatrelvir/ritonavir at day 0 was significantly associated with lower risks of post-acute mortality (hazard ratio [HR], 0.51 [95% confidence interval {CI}, 0.46 to 0.56], p value, <0·0001) and all-cause hospitalization (HR, 0.73 [95% CI, 0.70 to 0.77], p value, <0·0001) (Figure 3).

- In the control group, there were 22,312 patients.
- For the outcome of post-acute inpatient death, the number of events was 2,817, and the cumulative incidence (95% CI) on Day 365 was 14.18% (13.69, 14.67).
- For the outcome of post-acute all-cause hospitalization, the number of events was 10,372, and the cumulative incidence (95% CI) on Day 365 was 53.90% (53.18, 54.60).

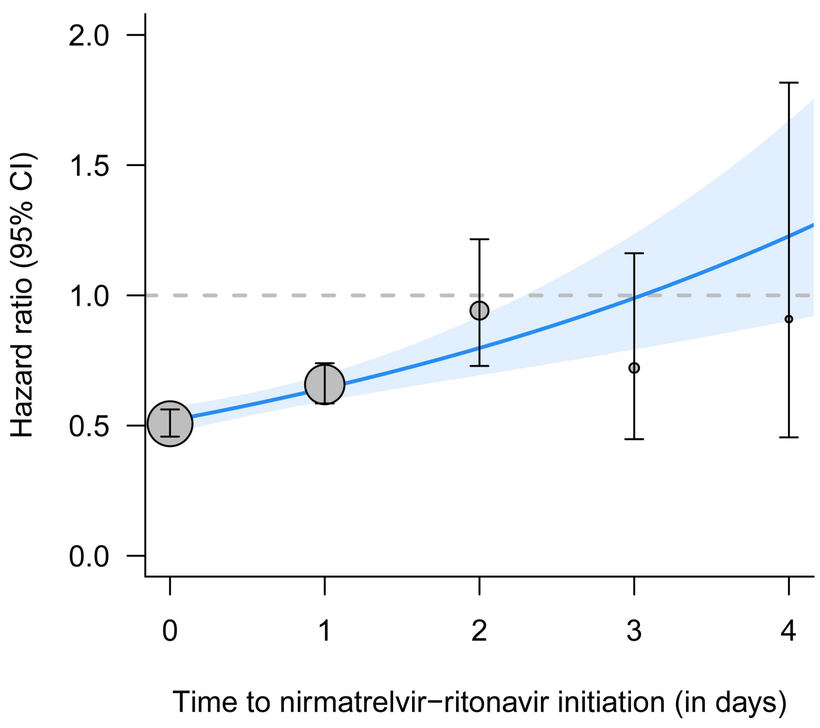

Figure 1. Association of time to nirmatrelvir/ritonavir initiation with hazard ratio for the outcome of death.

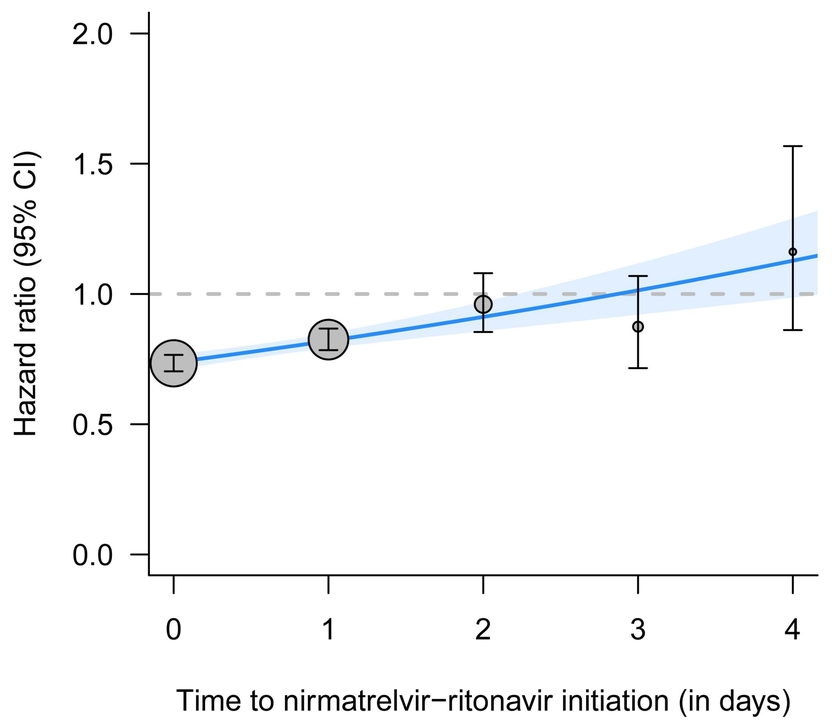

Figure 2. Association of time to nirmatrelvir/ritonavir initiation with hazard ratio for the outcome of all-cause hospitalization.

Outcome	Number treated	Number of events	Cumulative incidence (95% CI)	Adjusted HR (95% CI)	P value
Death					
Day 0	10028	618	6.36% (5.89, 6.86)	0.51 (0.46, 0.56)	<0.0001
Day 1	4973	381	7.91% (7.17, 8.70)	0.66 (0.59, 0.74)	<0.0001
Day 2 or later	977	104	11.09% (9.18, 13.21)	0.94 (0.77, 1.15)	0.55
All−cause hospitalization					
Day 0	10028	4265	44.21% (43.21, 45.20)	0.73 (0.70, 0.77)	<0.0001
Day 1	4973	2240	47.11% (45.67, 48.53)	0.82 (0.78, 0.87)	<0.0001
Day 2 or later	977	479	51.91% (48.61, 55.09)	0.99 (0.90, 1.09)	0.84

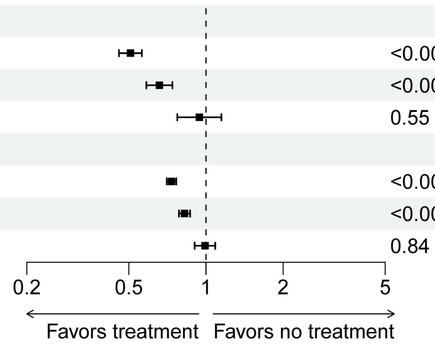

Figure 3. Associations with post-acute death and all-cause hospitalization stratified by different times to treatment initiation.

Conclusion

Our findings suggest that nirmatrelvir/ritonavir should be prescribed immediately after a COVID-19 diagnosis to maximize the benefits of antiviral treatment, not only in mitigating acute severity but also in reducing the risk of long COVID.