

Title:

COVID-19 rebound after Paxlovid treatment during Omicron BA.5 vs BA.2.12.1 subvariant predominance period

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Abstract

Paxlovid was authorized by FDA to treat mild-to-moderate COVID-19. In May 2022, the Centers for Disease Control and Prevention (CDC) issued a Health Alert Network Health Advisory on potential COVID-19 rebound after Paxlovid treatment. Since June 2022, Omicron BA.5 has become the dominant subvariant in the US, which is more resistant to neutralizing antibodies than the previous subvariant BA.2.12.1. Questions remain as to how COVID-19 rebound after Paxlovid treatment differs between the BA.5 and BA.2.12.1 subvariants. This is a retrospective cohort study of 15,913 patients who contracted COVID-19 between 5/8/2022-7/18/2022 and were prescribed Paxlovid within 5 days of their COVID-19 infection. The study population was divided into 2 cohorts: (1) BA.5 cohort (n=5,161) – contracted COVID-19 during 6/19/22-7/18/22 when BA.5 was the predominant subvariant². (2) BA.2.12.1 cohort (n=10,752) – contracted COVID-19 during 5/8/22-6/18/22 when the BA.2.12.1 was the predominant subvariant. The risks of both COVID-19 rebound infections and symptoms 2-8 days after Paxlovid treatment were higher in the BA.5 cohort than in the propensity-score matched BA.2.12.1 cohort: rebound infections (Hazard Ratio or HR: 1.32, 95% CI: 1.06-1.66), rebound symptoms (HR: 1.32, 95% CI: 1.04-1.68). As SARS-CoV-2 evolves with successive subvariants more evasive to antibodies, continuous vigilant monitoring is necessary for COVID-19 rebounds after Paxlovid treatment and longer time duration of Paxlovid treatment warrants evaluation.

Background

Paxlovid was authorized by FDA to treat mild-to-moderate COVID-19. In May 2022, the Centers for Disease Control and Prevention (CDC) issued a Health Alert Network Health Advisory on potential COVID-19 rebound after Paxlovid treatment¹. Since June 2022, Omicron BA.5 has become the dominant subvariant in the US². It is more resistant to neutralizing antibodies than the previous subvariant BA.2.12.1³. Questions remain as to how COVID-19 rebound after Paxlovid treatment differs between the BA.5 and BA.2.12.1 subvariants.

Objective

To compare COVID-19 rebound risks after Paxlovid treatments in patients who contracted COVID-19 during the BA.5 and BA.2.12.1 subvariant predominance period in the US.

Methods

We used the TriNetX Analytics COVID-19 Research Network platform that contains nationwide and real-time de-identified electronic health records (EHRs) of 98 million unique patients from 76 health care organizations with both inpatient and outpatient facilities across 50 states in the US⁴, covering diverse geographic locations, age groups, racial and ethnic groups, income levels and insurance types. TriNetX Analytics Platform performs statistical analyses on patient-level data and only reports on population level data and results without including protected health information (PHI) identifiers. MetroHealth System, Cleveland OH, Institutional Review Board determined that research using TriNetX is not Human Subject Research and therefore exempt from review. The study population comprised 15,913 patients age ≥ 12 years who contracted COVID-19 between 5/8/2022-7/18/2022 and were prescribed Paxlovid within 5 days of their COVID-19 infection. The study population was divided into 2 cohorts: (1) BA.5 cohort (n=5,161) – contracted COVID-19 during 6/19/22-7/18/22 when BA.5 was the predominant subvariant². (2) BA.2.12.1 cohort (n=10,752) – contracted COVID-19 during 5/8/22-6/18/22 when the BA.2.12.1 was the predominant subvariant².

We compared risks for COVID-19 rebound outcomes in BA.5 and BA.2.12.1 cohorts before and after propensity-score matching (1:1 matched using a nearest neighbor greedy algorithm with a caliper of 0.25 times the standard deviation) for covariates that are related to COVID-19 infections and outcomes⁵ (**Table 1** and **eMethod**). Rebound COVID-19 infections and symptoms (details in **eMethod**) during 2 to 8 days after Paxlovid treatment were followed and Kaplan-Meier survival analysis performed to estimate probability of outcomes. Cox's proportional hazards model was used to compare the two cohorts. Hazard ratio (HR) and 95% confidence intervals were used to describe the relative hazard of rebound outcomes based on comparison of time to event rates. All statistical tests were conducted within the TriNetX Advanced Analytics Platform on 8/4/2022 using R's Survival package, version 3.2-3. Details of the TriNetX database, covariates, propensity-score matching are in **eMethods**.

Findings

The BA.5 and BA.2.12.1 cohorts did not differ except that the BA.5 cohort comprised more Hispanics. After propensity-score matching, the two cohorts were balanced (**Table 1**). The cumulative risk of COVID-19 rebound infection 2-8 days after Paxlovid treatment was 2.81% and 3.42% in the BA.5 cohort and the BA.2.12.1 cohort respectively. The instantaneous risk of rebound symptoms was higher in the BA.5 cohort than in the BA.2.12.1 cohort (HR: 1.24, 95% CI: 1.01-1.53) but did not differ for rebound infections. After propensity-score matching, instantaneous risks of both rebound infections and symptoms were higher in the BA.5 cohort than in the matched BA.2.12.1 cohort: rebound infections (HR: 1.32, 95% CI: 1.06-1.66), rebound symptoms (HR: 1.32, 95% CI: 1.04-1.68) (**Figure 1**).

Discussion

The probability of COVID-19 rebound 2-8 days after Paxlovid treatment was higher in patients who contracted COVID-19 during the BA.5 than the BA.2.12.1 predominance period. As SARS-CoV-2 evolves with successive subvariants more evasive to antibodies, continuous vigilant monitoring is necessary for COVID-19 rebounds after Paxlovid treatment and longer time duration of Paxlovid treatment may be evaluated. Our study has several limitations: First, patient EHRs may be subject to over/mis/under-diagnosis and unmeasured confounders such as compliance with medication adherence and completion of treatment regimes. However, our comparison populations were both drawn from the TriNetX dataset, therefore these issues should not substantially affect the relative risk analyses. Second, patients in the TriNetX database may not necessarily represent the entire US population. Also, the accumulative risks of COVID-19 rebound documented in EHRs could be a substantial under-estimate of true prevalence, though this under-count should not substantially affect the comparison of instantaneous risks between the BA.5 and BA.2.12.1 cohorts. Nonetheless, results from our study need to be validated in other populations.

Contributors

RX conceived and designed the study and drafted the manuscript. LW performed data analysis and prepared tables and figures and participated in manuscript preparation. NDV, NAB, PBD, DCK critically contributed to study design, result interpretation and manuscript preparation. We confirm the originality of content. RX had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of interests

LW, NAB, PBD, DCK, NDV, RX have no financial interests to disclose.

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References

1. Centers for Disease Control and Prevention. Centers for Disease Control and Prevention. CDC HEALTH ADVISORY. COVID-19 Rebound After Paxlovid Treatment. Published May 24, 2022. Accessed August 4, 2022. https://emergency.cdc.gov/han/2022/pdf/CDC_HAN_467.pdf
2. Centers for Disease Control and Prevention. Centers for Disease Control and Prevention. COVID Data Tracker. Variant Proportions. Accessed August 4, 2022. <https://covid.cdc.gov/covid-data-tracker/#variant-proportions>
3. Wang Q, Guo Y, Iketani S, et al. Antibody evasion by SARS-CoV-2 Omicron subvariants BA.2.12.1, BA.4, & BA.5. *Nature*. Published online July 5, 2022. doi:10.1038/s41586-022-05053-w
4. TriNetX. TriNetX. Accessed August 4 2022. <https://trinetx.com/>
5. Centers for Disease Control and Prevention. Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Professionals. Centers for Disease Control and Prevention. Published June 15, 2022. Accessed August 4 2022. <https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html>

	Before Matching			After Matching		
	BA.5 cohort	BA.2.12.1 cohort	SMD	BA.5.4 cohort	BA.2.12.1 cohort	SMD
Total number	5,161	10,752		5,142	5,142	
Age at index event (years, mean±SD)	55.6±17.0	55.8 ± 16.7	0.009	55.6±17.0	55.7± 16.4	0.003
Sex (%)						
Female	61.3	60.4	0.02	61.3	60.4	0.02
Male	38.6	39.6	0.02	38.7	39.5	0.02
Ethnicity (%)						
Hispanic/Latinx	6.4	4.4	0.10*	6.3	5.5	0.03
Not Hispanic/Latinx	81.3	67.9	0.31*	81.3	83.2	0.05
Unknown	12.3	27.9	0.40*	12.3	11.3	0.03
Race (%)						
Asian	2.0	2.0	0.002	2.0	2.1	0.005
Black	7.7	7.7	0.001	7.6	6.7	0.04
White	82.1	82.8	0.02	82.1	82.8	0.02
Unknown	8.0	7.3	0.02	7.9	8.1	0.008
Adverse socioeconomic determinants of health (%)	7.1	7.6	0.02	7.1	7.4	0.01
Pre-existing medical conditions and treatments (%)						
Heart diseases	13.2	13.0	0.005	13.2	13.2	0.001
Cancer	43.2	42.8	0.004	43.0	43.8	0.02
Hypertension	47.1	45.5	0.03	47.0	46.1	0.02
Cerebrovascular diseases	7.9	8.0	0.004	7.8	8.0	0.005
Chronic lower respiratory diseases	30.5	30.1	0.009	30.6	30.2	0.008
Chronic kidney diseases	6.0	8.0	0.05	6.7	6.7	0.003
Liver diseases	11.1	11.6	0.02	11.1	10.4	0.02
Overweight and obesity	32.8	30.4	0.05	32.7	31.3	0.03
Type 2 diabetes	19.2	18.4	0.02	19.6	19.3	0.007
Disorders involving the immune mechanisms	3.4	3.6	0.007	3.4	3.3	0.008
Congenital	11.2	12.5	0.04	11.2	11.3	0.002

disorders						
Mood disorders including depression	27.5	27.8	0.007	27.5	26.8	0.02
Psychotic disorders	1.2	1.5	0.03	1.2	1.2	0.002
Behavioral disorders	4.7	5.0	0.02	4.7	4.8	0.003
Substance use disorders	16.4	14.6	0.05	16.5	15.7	0.02
Alzheimer's disease	0.5	0.4	0.006	0.4	0.6	0.02
HIV	1.1	1.5	0.03	1.1	1.3	0.01
Thalassemia	0.3	0.5	0.02	0.4	0.3	0.003
Organ Transplant	0.8	0.6	0.02	0.8	0.6	0.01
Tobacco smoker	8.9	7.6	0.05	8.9	8.2	0.02
Immunosuppressants	5.2	5.2	0.001	5.2	5.4	0.01
COVID-19 vaccine documented in EHRs (%)	23.6	22.7	0.01	23.5	22.1	0.03

Table 1. Characteristics of the study population before and after propensity-score matching (1:1 matching based on greedy nearest-neighbour matching with a caliper of 0.25 x standard deviation). BA.5 cohort – who contracted COVID-19 during 6/19/22-7/15/22 when the BA.5 was the predominant subvariant in the US and were prescribed Paxlovid within 5 days of their COVID-19 infection. BA.2.12.1 cohort – who contracted COVID-19 during 5/8/22-6/18/22 when the BA.2.12.1 was the predominant subvariant and were prescribed Paxlovid within 5 days of their COVID-19 infection. The status for adverse socioeconomic determinants of health, medical conditions, immunosuppressant usage, organ transplants, and EHR-based COVID-19 vaccination status were based on presences of related codes in patients' EHRs anytime up to 1 day before Paxlovid treatment. SMD – standardized mean differences. *SMD greater than 0.1, a threshold being recommended for declaring imbalance.

COVID-19 rebounds after Paxlovid treatment during Omicron BA.5 vs BA.2.12.1 subvariant predominance period

Rebound outcome	BA.5 (n=5,161)	BA.2.12.1 (n=10,752)	HR (95% CI)
Before matching			
COVID-19 infection	2.81%(145/5,161)	3.42%(368/10,752)	1.15 (0.95–1.40)
COVID-19 symptoms	2.42%(125/5,161)	2.87%(309/10,752)	1.24 (1.01–1.53)
After matching			
COVID-19 infection	2.80%(144/5,142)	3.31%(170/5,142)	1.32 (1.06–1.66)
COVID-19 symptoms	2.39%(123/5,142)	2.98%(153/5,142)	1.32 (1.04–1.68)

←--slower rebound for BA.5.4 Hazard Ratio faster rebound for BA.5.4--→

Figure 1. COVID-19 rebounds 2-8 days after Paxlovid treatment between the BA.5 and BA.2.12.1 cohorts before and after propensity-score matching.