Hospitalization and Emergency Department Encounters for COVID-19 After Paxlovid Treatment — California, December 2021–May 2022

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Nirmatrelvir/ritonavir (Paxlovid) is a combination protease inhibitor that blocks replication of SARS-CoV-2 (the virus that causes COVID-19) and has been shown to reduce the risk for hospitalization and death among patients with mild to moderate COVID-19 who are at risk for progression to severe disease* (*1*). In December 2021, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for early treatment with Paxlovid among persons with mild to moderate cases of COVID-19 who are at high risk for progression to severe disease (*2*). FDA and a small number of published case reports have documented recurrence of COVID-19 symptoms or a positive viral test result (COVID-19 rebound) 2–8 days after recovery or a negative SARS-CoV-2 test result among patients treated with Paxlovid (*3*–*7*); however, large-scale studies investigating severe illness after Paxlovid treatment are limited. This study used electronic health record (EHR) data from a large integrated health care system in California (Kaiser Permanente Southern California [KPSC]) to describe hospital admissions and emergency department (ED) encounters related to SARS-CoV-2 infections during the 5–15 days after pharmacy dispensation of a 5-day treatment course of Paxlovid. Among 5,287 persons aged ≥12 years who received Paxlovid during December 31, 2021–May 26, 2022, 73% had received ≥3 doses of COVID-19 vaccine†, and 8% were unvaccinated. During the 5–15 days after Paxlovid treatment was dispensed, six hospitalizations and 39 ED encounters considered to be related to SARS-CoV-2 infection were identified, representing <1% of all patients to whom Paxlovid treatment was dispensed during the study period. Among these 45 persons, 21 (47%) were aged ≥65 years, and 35 (78%) had at least one underlying medical condition§ (*8*). This study found that hospitalization or ED encounters for COVID-19 during the 5–15 days after Paxlovid treatment was dispensed for mild to moderate COVID-19 illness were rarely identified. When administered as an early-stage treatment, Paxlovid might prevent COVID-19–related hospitalization among persons with mild to moderate cases of COVID-19 who are at risk for progression to severe disease.

Clinical and demographic characteristics from EHRs were described among patients receiving Paxlovid during December 31, 2021–May 26, 2022, within KPSC, a large integrated health care system in California. KPSC facilities include 15 large medical centers that provide care to approximately 4.6 million members across southern California. All hospital admissions and ED encounters during the 5–15 days after Paxlovid treatment was dispensed¶ were flagged for medical chart review to confirm that the hospitalization or ED encounter was related to COVID-19.** Patients identified with two Paxlovid prescriptions ≥14 days apart were followed for 5–15 days after each prescription date. For patients with both a documented hospital admission and an ED encounter during the 5–15 days after the date that Paxlovid was dispensed, the hospital admission was included in the analysis. Data analyses were performed using SAS software (version 9.4; SAS Institute). This activity was reviewed by CDC and was conducted consistent with applicable federal law and CDC policy.†† This activity was also reviewed and approved by KPSC Institutional Review Board.

* Persons eligible for treatment with Paxlovid include those aged ≥12 years, weighing ≥88 lbs (40 kg), with a positive SARS-CoV-2 test result, mild or moderate symptoms, not requiring hospitalization because of severe or critical COVID-19 illness at the time of treatment initiation, and the presence of at least one risk factor that can predispose them to severe disease (https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html), without evidence of severe renal or hepatic impairment. https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/ritonavir-boosted-nirmatrelvir--paxlovid-/

† COVID-19 vaccine doses were categorized ≥14 days before the Paxlovid dispense date as follows: 4 doses = receipt of a fourth COVID-19 vaccine dose; 3 doses = receipt of a third COVID-19 vaccine dose ≥28 days after the second dose (and no fourth dose received); 2 doses = receipt of a second COVID-19 vaccine dose (and no third dose received); 1 dose = receipt of a single COVID-19 vaccine dose (and no second dose received); 0 = unvaccinated.

§ Underlying medical conditions were defined according to the modified Charlson Comorbidity Index, which included 17 conditions of interest available in EHRs during the 12 months preceding the date of treatment. Conditions included immunosuppressive disorders, acute myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, rheumatoid disease, peptic ulcer disease, mild and moderate liver disease, severe liver disease, diabetes with severe complications, diabetes without severe complications, hemiplegia or paraplegia, renal disease, cancer, and HIV/AIDS.

¶ Patients were considered to have received treatment with Paxlovid if they had documentation of a pharmacy dispensation of Paxlovid in their EHRs.

** Patients were considered to have a confirmed COVID-19–related hospital admission or ED encounter if their EHRs indicated that COVID-19 was either the primary reason for the encounter or if there was documentation of symptoms consistent with COVID-19 according to the latest CDC definition. https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html

†† 45 C.F.R. part 46, 21 C.F.R. part 56; 42 U.S.C. Sect. 241(d); 5 U.S.C. Sect. 552a; 44 U.S.C. Sect. 3501 et seq.

Summary

What is already known about this topic?

Recurrence of COVID-19 symptoms and positive SARS-CoV-2 test results have been reported after completion of Paxlovid oral antiviral treatment for COVID-19, but real-world evidence of severe illness following Paxlovid is lacking.

What is added by this report?

COVID-19–related hospital admissions and emergency department (ED) encounters occurring 5–15 days after Paxlovid treatment were described using data from a large integrated health care system. Reports of such hospitalizations or ED encounters occurred infrequently, representing <1% of Paxlovid-treated patients over the study period.

What are the implications for public health practice?

When administered as an early-stage treatment, Paxlovid might prevent COVID-19–related hospitalization among persons with mild-to-moderate COVID-19 who are at risk for progression to severe disease.

During December 31, 2021–May 26, 2022, a total of 5,287 persons aged ≥12 years received a prescription for Paxlovid, including four (<0.1%) who received two Paxlovid prescriptions ≥14 days apart. Among these 5,287 persons, 3,025 (57.2%) were female, and the median age was 61 years (Table). The largest percentage of persons (2,245; 42.5%) identified as non-Hispanic White, and 30.3% (1,603) identified as Hispanic. A total of 2,999 (56.7%) Paxlovid recipients had at least one underlying medical condition. Overall, 4,875 (92.2%) persons had received at least 1 COVID-19 vaccine dose; most (3,836; 72.5%) received at least 3 doses, and 937 (17.7%) received 2 doses at least 14 days before the date of Paxlovid prescription; a total of 412 (7.8%) Paxlovid recipients were unvaccinated.

During the 5–15 days after treatment was dispensed, six (0.11%) hospitalizations and 39 (0.74%) ED encounters among persons with symptoms consistent with COVID-19 were identified, representing <1% of all patients who received Paxlovid during the study period; three hospitalizations and 10 ED encounters had a COVID-19 diagnosis code or positive SARS-CoV-2 test result documented in the associated EHR. Twenty-one (46.7%) of these 45 patients were aged ≥65 years and 35 (77.8%) had at least one documented underlying medical condition. A higher proportion of those identified with COVID-19–related hospitalizations or ED encounters were either unvaccinated or vaccinated with 1 dose of COVID-19 vaccine (eight of 45; 17.8%) compared with all treated patients (514 of 5,287; 9.7%). Among the six hospitalized patients, five had received 3 doses of COVID-19 vaccine and one had received a single vaccine dose. All hospitalized patients had comorbidities or were of advanced age (range = 61–104 years), which put them at increased risk for severe COVID-19. Two hospitalized patients died; both were at high risk for severe illness because of multiple comorbidities and age, and their deaths were attributed to underlying disease. The remaining four hospitalized patients recovered, as did the 39 patients with COVID-19–related ED encounters during the 5–15 days after Paxlovid was dispensed.

Discussion

In this analysis of data from patients aged ≥12 years in a large integrated health care system who received Paxlovid treatment during December 2021–May 2022, hospitalizations or ED encounters for COVID-19–related illness during the 5–15 days after Paxlovid dispensation occurred among <1% of all patients. The rarity of these outcomes is consistent with evidence from recent case reports and large observational studies, which found that symptoms experienced by patients with COVID-19 rebound after treatment with Paxlovid are milder than those experienced during the primary infection (*3*–*5*) and are unlikely to lead to hospitalization (*9*,*10*).

The recurrence of symptoms might represent part of the natural history of SARS-CoV-2 infection in some persons, irrespective of treatment or vaccination status (*6*). Although little is known about the severity of COVID-19 rebound symptoms, it has been suggested that very early treatment with Paxlovid might transiently suppress viral replication before natural immunity is sufficient to complete viral clearance (*3*). This might allow for a short interval during which rebound-associated increases in SARS-CoV-2 viral load might be observed. However, the findings from the current study among approximately 5,000 eligible COVID-19 patients treated with Paxlovid suggest that responses (whether treatment-mediated, immune-mediated, or a combination of both) might be sufficient to prevent severe outcomes, including hospitalization, for most patients.

The recurrence of COVID-19 symptoms after Paxlovid treatment might also be related to other factors, including viral reinfection or the emergence of treatment-resistant mutations. In the current study, recovery from initial infection was not assessed and viral sequencing was not performed on specimens before and after treatment initiation; therefore, the distinction between progression of initial illness, COVID-19 rebound, or reinfection could not be made. However, in the limited studies that have obtained sequence data, similarity of viral strains between pre- and posttreatment specimens suggested that reinfection was unlikely, at least in the small number of patients studied (*4*). In addition, research conducted by FDA demonstrated that viral rebound in several subjects was not associated with known resistance mutations, although these analyses are ongoing (*7*).

TABLE. Characteristics of persons aged ≥12 years prescribed Paxlovid treatment, by COVID-19–related hospitalizations or emergency department encounters 5–15 days after treatment dispensation among members of a large integrated health care system — California, December 31, 2021–May 26, 2022

Characteristic	No. (column %)	
	All Paxlovid recipients	COVID-19–related* hospitalization/ED encounter 5–15 days after Paxlovid dispensed†
Total, row %	**5,287**	**45 (0.9)**
Age group, yrs§		
12–17	36 (0.7)	0 (—)
18–24	81 (1.5)	0 (—)
25–44	994 (18.8)	11 (24.4)
45–64	1,929 (36.5)	12 (26.7)
≥65	2,214 (41.9)	21 (46.7)
Unknown	33 (0.6)	1 (2.2)
Median (IQR)	61 (47.0–71.0)	63 (44.5–77.0)
Sex§		
Female	3,025 (57.2)	30 (66.7)
Male	2,228 (42.1)	14 (31.1)
Unknown	34 (0.6)	1 (2.2)
Race and ethnicity§		
White, non-Hispanic	2,245 (42.5)	16 (35.6)
Hispanic	1,603 (30.3)	14 (31.1)
Asian or Pacific Islander, non-Hispanic	823 (15.6)	8 (17.8)
Black, non-Hispanic	327 (6.2)	4 (8.9)
Multiple or other	119 (2.3)	1 (2.2)
Unknown	170 (3.2)	2 (4.4)
Charlson comorbidity index¶		
0	2,288 (43.3)	10 (22.2)
1	1,321 (25.0)	13 (28.9)
2	737 (13.9)	6 (13.3)
≥3	941 (17.8)	16 (35.6)
No. of COVID-19 vaccine doses received**		
0	412 (7.8)	5 (11.1)
1	102 (1.9)	3 (6.7)
2	937 (17.7)	9 (20.0)
3	3,279 (62.0)	27 (60.0)
4	557 (10.5)	1 (2.2)

Abbreviations: ED = emergency department; EHR = electronic health record.

* Patients were considered to have a confirmed COVID-19–related hospitalization or ED encounter if their EHRs indicated documentation of known symptoms consistent with COVID-19 illness.

† Patients were considered to have received treatment with Paxlovid if their EHR contained documentation of a pharmacy dispensation of Paxlovid.

§ At the date of treatment dispensation.

¶ The weighted Charlson Comorbidity Index included 17 conditions of interest available in EHRs from the 12 months preceding the date of treatment. Conditions included immunosuppressive disorders, acute myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, rheumatoid disease, peptic ulcer disease, mild and moderate liver disease, severe liver disease, diabetes with severe complications, diabetes without severe complications, hemiplegia or paraplegia, renal disease, cancer, and HIV/AIDs.

** COVID-19 vaccine doses were categorized ≥14 days before the Paxlovid dispense date as follows: 4 doses = receipt of a fourth COVID-19 vaccine dose; 3 doses = receipt of a third COVID-19 vaccine dose ≥28 days after the second dose (and no fourth dose received); 2 doses = receipt of a second COVID-19 vaccine dose (and no third dose received); 1 dose = receipt of a single COVID-19 vaccine dose (and no second dose received); 0 = unvaccinated.

The findings in this report are subject to at least five limitations. First, COVID-19–related hospital admissions and ED encounters among patients with symptoms consistent with COVID-19 illness were used as proxy indicators of COVID-19 disease severity; these instances might include admissions and encounters for persons seeking care for unrelated conditions. Although medical chart reviews were conducted to verify that COVID-19–related illness or symptoms were potentially a primary reason for these health care encounters, misclassification might have occurred because of the nonspecific nature of COVID-19–related symptoms. Second, there was no control population of persons who did not receive treatment with Paxlovid for mild to moderate COVID-19, and therefore the relative benefit of treatment with Paxlovid could not be determined, nor could it be distinguished from the overall benefit of receiving COVID-19 vaccination. However, data from randomized controlled trials and from large-scale observational studies have demonstrated a protective effect of Paxlovid on COVID-19–associated hospitalization and death (*1*,*9*,*10*), albeit sometimes with notably different study populations that differed by age or vaccination status. Third, data on treatment initiation and adherence were not systematically collected; therefore, persons with

incomplete treatment might have been misclassified as having completed a full course of Paxlovid. Fourth, patients might have sought care within ED settings because of convenience rather than acuity of illness. However, these last two limitations would have led to an overestimation of acute COVID-19 illness after Paxlovid dispensation, which strengthens the conclusion that such events are rare. Finally, although members typically seek care at KPSC, and KPSC receives a regular data feed from the California Immunization Registry on outside vaccinations, data on Paxlovid prescriptions dispensed or vaccinations administered by non-KPSC providers might be incomplete.

This study found that <1% of patients treated with Paxlovid were identified with COVID-19–related hospitalization or ED encounters 5-15 days after treatment was dispensed. When administered as an early-stage treatment, Paxlovid might prevent COVID-19–related hospitalization among persons with mild to moderate COVID-19 cases who are at risk for progression to severe disease. Additional research is warranted to provide further understanding of the apparent association between Paxlovid and reduced risk for severe COVID-19 illness, including studies with control groups and more precise indicators of COVID-19 illness severity.

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