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Coronavirus Pandemic

Outcome differences of starting Paxlovid for COVID-19 within or after five days of symptoms onset in the elderly: a retrospective study

Junjun Chen[1 #], Quanjun Yang[1 #], Xiaohong Xu[1], Xia Wu[1], Yonglong Han[1], Cheng Guo[1], Jiao Yang[1]

[1] *Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China*

# Authors contributed equally to this work.

Abstract

Introduction: The study aimed to compare the outcomes of nirmatrelvir and ritonavir drug combination (Paxlovid) therapy in patients who received treatment within or after five days of COVID-19 confirmed in the elderly.

Methodology: This was a single-center, retrospective cohort study of older COVID-19 patients (≥ 60 years) admitted from April 7 to May 30, 2022. Patients were categorized into the EP group (starting Paxlovid within five days) and the LP group (starting Paxlovid after five days) following symptoms onset. Length of stay and positive SARS-CoV-2 duration were compared between the two groups. Severe case conversion from mild and moderate COVID-19 patients were also analyzed.

Results: In total, 273 patients were included: 137 in the EP group and 136 in the LP group. Compared to the LP group, the EP group had a significantly shorter length of stay (12.4 vs. 14.7 days, $p = 0.001$) and positive SARS-CoV-2 duration (11.7 vs. 15.8 days, $p < 0.001$). The EP group had lower severe case conversion (4.4% vs. 15.4%, $p = 0.002$). Additionally, abnormal IL-6 and lower lymphocyte count indicated increased length of stay. Older age was associated with a decreased risk in SARS-CoV-2 negative test (HR = 0.98) and an increased risk in severe case conversion (OR = 1.11).

Conclusions: Starting Paxlovid within five days of COVID-19 symptoms onset reduced the length of stay and SARS-CoV-2 duration compared to initiating treatment after five days. While severe case conversion among mild COVID-19 patients might be comparable whether starting Paxlovid within or after five days.

Key words: Paxlovid; COVID-19; length of stay; SARS-CoV-2.

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Introduction

Since the end of 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused a global pandemic of coronavirus disease 2019 (COVID-19). It remains a serious threat to human health and an overwhelming financial burden on patients' families and healthcare systems [1]. According to the World Health Organization (WHO), the cumulative number of global confirmed COVID-19 cases had exceeded 761 million as of March 2023. The average mortality rate was approximately 0.9%, resulting in more than 6.8 million deaths [2]. In severe cases, respiratory failure, shock, renal insufficiency, blood coagulation disorder, and other related complications could occur [3].

Efforts are underway to stem the SARS-CoV-2 pandemic worldwide. Vaccines against COVID-19, monoclonal antibodies, antivirals, and immunomodulatory agents have been developed and adopted [4,5]. Paxlovid is a new oral antiviral medication that was granted an Emergency Use Authorization (EUA) by the US Food and Drug Administration (FDA) for outpatient treatment and regarding pediatric population (older than 12 years of age and BW > 40 kg) of mild to moderate COVID-19. The package inserts and current guidelines for Paxlovid indicate that Paxlovid treatment should be initiated as soon as possible following a diagnosis of COVID-19 and within five days of symptoms onset. On February 11, 2022, Paxlovid was conditionally approved by the National Medical Products Administration (NMPA) for import registration in China for the treatment of mild to moderate COVID-19 in adults. Paxlovid was also the only oral antiviral recommended in the "COVID-19 Diagnosis and Treatment Guidelines (9th edition)" for the treatment of mild to moderate COVID-19 patients who are at risk for progression to severe disease. PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets. Nirmatrelvir blocks SARS-CoV-2 protease activity, which is required for virus replication. Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir, resulting in increased plasma concentrations of nirmatrelvir [6]. Before the advent of

Paxlovid, antiviral treatments of COVID-19 in China usually used a combination of antiviral agents, including α-interferon, ribavirin, phosphate chloroquine, and abidol hydrochloride with traditional Chinese medicine [7,8].

The initial clinical trial has shown that Paxlovid is 89% effective in patients at risk of serious illness due to COVID-19 [9]. Paxlovid has also subsequently been shown to reduce the risk of hospitalization and death among patients with mild to moderate COVID-19 who are at risk for progression to severe disease [10,11]. A study from Israel suggests that treatment with Paxlovid is associated with a prominent reduction in severe COVID-19 cases and mortality in the era of Omicron, especially among older patients [12]. In addition, a multicenter study also demonstrated that the use of Paxlovid in elderly patients may promote recovery from COVID-19 and reduce the viral load without adverse events [13]. However, those studies excluded patients who received Paxlovid after five days following symptoms onset. Real-world evidence regarding the benefit of Paxlovid in COVID-19 patients who started Paxlovid treatment five days following the onset of their symptoms, especially for older patients, is limited. The current analysis will provide evidence on the outcome differences of Paxlovid therapy in COVID-19 patients who received Paxlovid treatment within or after five days of symptoms onset, with a focus on older patients.

The current study aimed to compare the outcomes of Paxlovid therapy in patients who received Paxlovid treatment within or after five days of a confirmed diagnosis of COVID-19 with symptoms onset in adults 60 years of age or older. This study was approved by the Ethics Committee of Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine (No. 2022-KY-060(K), approval data May 20, 2022).

Methodology

Study design and participants

This study was a retrospective cohort study, of COVID-19 patients who received Paxlovid treatment at the Shanghai Sixth People's Hospital from April 7 to May 30, 2022. The diagnosis of COVID-19 was based on the "COVID-19 Diagnosis and Treatment Guideline" published by the China National Health Commission (NHC). Inclusion criteria were 1) older patients (≥ 60 years) with a mild to moderate diagnosis of COVID-19 confirmed by SARS-CoV-2 real-time polymerase chain reaction (RT-PCR), and 2) patients who were hospitalized for the first time due to COVID-19. Exclusion criteria were patients who 1) received Paxlovid more than 14 days after the confirmed diagnosis of COVID-19 and 2) had other viral pneumonia or were undergoing dialysis.

Based on the time that patients who received Paxlovid therapy after a confirmed diagnosis of COVID-19 with symptoms onset, patients were grouped into the early Paxlovid treatment group (EP group, received Paxlovid ≤ 5 days after symptoms onset) and late Paxlovid treatment group (LP group, received Paxlovid > 5 days after symptoms onset).

Data collection

Demographic data (age, sex) and clinical information were collected. The severity of COVID-19 disease was determined according to the China NHC "COVID-19 Diagnosis and Treatment Guidelines", which conform to the guidelines provided by the WHO [14]. The severity of the disease was categorized into mild and moderate. Clinical information included COVID-19 diagnosis and severity, nucleic acid CT value at admission, comorbidities, SARS-CoV-2 vaccination status, Paxlovid treatment data, the time of two consecutive negative SARS-CoV-2 RNA tests, and laboratory parameters. The following laboratory parameters were collected: C-reactive protein (CRP), white blood cell (WBC), interleukin 6 (IL-6), lymphocyte, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), total bilirubin (TBIL), blood urea nitrogen (BUN), serum creatinine (SCR), and uric acid (UA).

Study outcomes

The primary outcomes were the length of stay and the positive SARS-CoV-2 duration (the time from the initial positive test to the second consecutive negative test with RT-PCR). Secondary outcomes encompassed the rate of severe case conversion (from mild or moderate COVID-19 to severe or critically ill cases). Subgroup analyses of the treatment outcomes of Paxlovid were performed according to the COVID-19 severity classification.

Sample size calculation

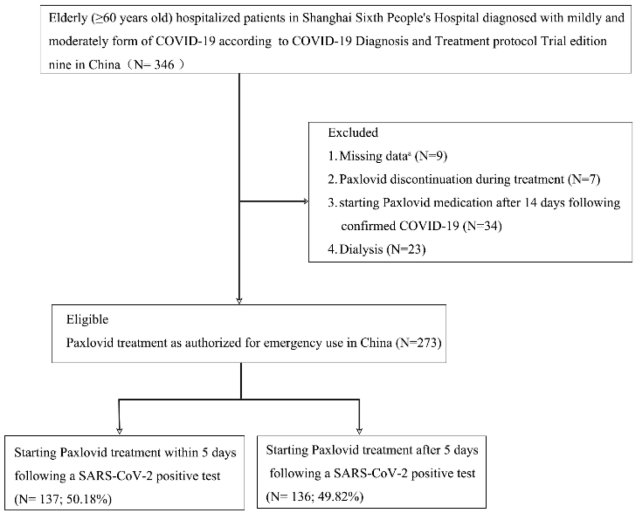
This study included patients with mild and moderate COVID-19 who were admitted to the hospital and were assigned to groups based on the timing of starting Paxlovid therapy following symptoms onset.

Statistical analysis

Categorical variables are presented with numbers and proportions. Continuous variables with normal

distribution are presented with means and standard deviations, and those with non-normal distribution are expressed as medians. Continuous data were analyzed using bivariate Student's t-tests or the Wilcoxon rank sum test. Categorical data were analyzed with the chi-square test or Fisher's exact test. Multivariate Cox proportional hazard regression models were used to evaluate significant variables associated with hospital discharge and the SARS-CoV-2 negative test using the hazard ratio (HR) and the 95% confidence interval (CI). Significant predictors for conversion to severe cases were included for multivariate logistic regression modeling integrating the odds ratio (OR) with 95% CI. A value of $p < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS 22.0 and Graphpad Prism 9.0.

Figure 1. Patient flow diagram.



a: Records were missing the onset date of coronavirus disease 2019 (COVID-19) symptoms because of transfer to another hospital or uncomplete records.

Table 1. Baseline demographics and characteristics.

Demographic and clinical characteristics	EP group (Start Paxlovid treatment within 5 days of symptoms onset) (n = 137)	LP group (Start Paxlovid treatment after 5 days of symptoms onset) (n = 136)	*p*
Age, yr	76.7 (9.9)	76.6 (10.2)	0.902
By category			
60-80, n	88 (64.2%)	84 (61.8%)	0.673
>80, n	49 (35.8%)	52 (38.2%)	
Gender			
Female, n	77 (56.2%)	62 (45.6%)	0.079
Male, n	60 (43.8%)	74 (54.4%)	
Laboratory indicators			
CRP, mg/L	20.5 (29.3)	20.9 (28.9)	0.907
WBC, 10^3/μL	5.9 (2.6)	5.8 (2.3)	0.548
IL-6, pg/mL	25.3 (45.1)	33.1 (65.5)	0.275
Lymphocyte, 10^3/μL	1.3 (0.60)	1.7 (3.9)	0.162
ALT, U/L	22.0 (13.9)	20.2 (18.7)	0.357
AST, U/L	36.6 (57.1)	29.7 (25.2)	0.199
ALP, U/L	85.2 (47.5)	79.8 (33.7)	0.325
TBIL, μmol/L	12.6 (7.5)	11.7 (4.3)	0.439
BUN, mmol/L	7.2 (7.6)	6.6 (3.2)	0.386
SCR, μmol/L	82.7 (63.0)	80.6 (37.2)	0.771
UA, μmol/L	310.4 (148.0)	323.4 (108.2)	0.518
SARS-CoV-2 CT value			
ORF1ab gene	23.9 (5.9)	23.7 (5.2)	0.770
N gene	22.7 (6.9)	22.5 (6.0)	0.786
Clinical classification			
Mild, n	35 (25.5%)	31 (22.8%)	0.595
Moderate, n	102 (74.5%)	105 (77.2%)	
Comorbidities			
Diabetes, n	41 (29.9%)	29 (21.3%)	0.104
Hypertension, n	78 (56.9%)	74 (54.4%)	0.675
Cardiovascular disease, n	47 (34.3%)	40 (29.4%)	0.386
Chronic liver disease, n	0 (0)	3 (2.3%)	-
Chronic lung disease, n	15 (10.9%)	23 (16.9%)	0.155
Chronic kidney disease, n	2 (1.5%)	6 (4.4%)	0.148
Neurological disease, n	48 (35.0%)	46 (33.8%)	0.833
Malignancy, n	12 (8.8%)	14 (10.3%)	0.666
COVID-19 vaccination, n	27 (19.7%)	22 (16.2%)	0.447
Paxlovid administration, days	5.7 (1. 2)	5.7 (1.4)	0.661
Starting Paxlovid after symptoms onset, days	3.0 (1.3)	9.3 (2.5)	< 0.001

Data are presented as the mean (SD) or number (percentage). CRP: C reactive protein; WBC: white blood cell; ALT: alanine transaminase; AST: aspartate transaminase; ALP: alkaline phosphatase; TBIL: total bilirubin; BUN: blood urea nitrogen; SrCR: Serum creatinine; UA: Uric Acid.

Table 2. Comparison of the treatment outcome.

Clinical outcome	EP group (Starting Paxlovid treatment within 5 days of symptoms onset) (n = 137)	LP group (Starting Paxlovid treatment after 5 days of symptoms onset) (n = 136)	*p*
Length of stay, days	12.4 (5.5)	14.7 (5.0)	0.001
Positive SARS-CoV-2 duration, days	11.7 (5.1)	15.8 (4.9)	< 0.001
Severe case conversion, n	6 (4.4%)	21 (15.4%)	0.002

Results

The characteristics of patients

A total of 346 patients with confirmed COVID-19 infections were hospitalized, of which 273 were eligible for analysis (Figure 1). These patients were assigned to the EP group (50.18%, 137/273) and the LP group (49.82%, 136/273). There were no statistically significant differences in sex, age, laboratory indicators (CRP, WBC, IL-6, Lymphocyte, ALT, AST, ALP, TBIL, BUN, SCR, and UA), CT values of SARS-CoV-2 and clinical classification.

The most common comorbidity in both groups was hypertension, with 56.9% (78/137) in the EP group and 54.4% (74/136) in the LP group. Most of the patients had moderate severity of COVID-19: 74.5% (102/137) in the EP group and 77.2% (105/136) in the LP group. However, the proportion of patients with mild or moderate COVID-19 did not differ significantly between the two treatment groups.

The mean start time for Paxlovid treatment after symptoms onset was 3.0 days in the EP group, compared to 9.3 days in the LP group ($p < 0.001$). The mean duration of Paxlovid treatment was 5.7 days in the two groups ($p = 0.661$). Details are shown in Table 1.

Primary and secondary outcomes

Compared to the LP group, the EP group had a significantly shorter length of stay (12.4 vs. 14.7 days, $p = 0.001$) and a shorter positive SARS-CoV-2 duration (11.7 vs. 15.8 days, $p < 0.001$), respectively. The EP group had a lower rate of severe case conversion compared to the LP group (4.4% vs. 15.4%, $p = 0.002$). Details are shown in Table 2 and Figure 2.

Figure 2. Starting Paxlovid treatment within 5 days after COVID-19 symptoms onset shortens the length of stay and improves viral negative conversion. The p for treatment effect was assessed using the Log-rank test.

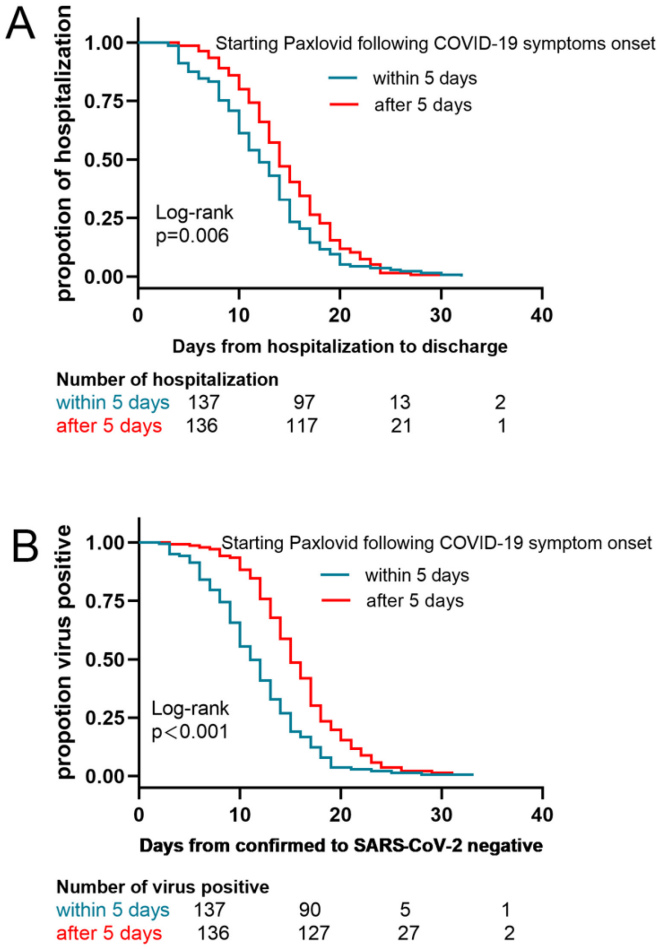


Table 3. Subgroup analysis of the treatment outcomes of Paxlovid according to the COVID-19 classification.

	EP group (Starting Paxlovid within 5 days of symptom onset) (n = 137)	LP group (Starting Paxlovid after 5 days of symptom onset) (n = 136)	*p*
Mild	35	31	
Length of stay, days	11.5 (4.7)	14.1 (3.4)	0.014
Positive SARS-CoV-2 duration, days	10.9 (4.3)	14.2 (3.6)	0.002
Severe case conversion, n	1 (2.9)	5 (16.1)	0.061
Moderate	102	105	
Length of stay, days	12.8 (5.8)	14.9 (5.3)	0.007
Positive SARS-CoV-2 duration, days	12.0 (5.3)	16.3 (4.9)	< 0.001
Severe case conversion, n	1 (0.98)	20 (19.0)	< 0.001

Subgroup analysis

In patients with mild COVID-19, the EP group had a significantly shorter length of stay compared to the LP group (11.5 vs. 14.1 days, $p = 0.014$) and positive SARS-CoV-2 duration (10.9 vs. 14.2 days, $p = 0.002$). In patients with moderate COVID-19, the EP group had a significantly shorter length of stay compared to the LP group (12.8 vs. 14.9 days, $p = 0.007$) and positive SARS-CoV-2 duration (12.0 vs. 16.3 days, $p < 0.001$).

The rate of severe case conversion was also significantly lower in the EP group than in the LP group (0.98% vs. 19.0%, $p < 0.001$). Details are shown in Table 3.

Factors affecting the effectiveness of Paxlovid treatment

The multivariate Cox regression model showed that starting Paxlovid treatment within five days was independently associated with a statistically significant increase in hospital discharge with an HR of 1.31 (95% CI 1.00-1.71), indicating a shorter length of stay. The lower incidence rate of hospital discharge was likely attributed to abnormal IL-6 levels (HR 0.70, 95% CI 0.51-0.95) and lower lymphocyte count (HR 0.75, 95% CI 0.58-0.99). Details are shown in Figure 3.

The results of the multivariate Cox regression model for the negative SARS-CoV-2 test were consistent with the results of hospital discharge with an HR of 2.01 (95% CI 1.54-2.62) in patients who started Paxlovid treatment within five days. In elderly COVID-19 patients, older age was associated with a decreased incidence of the SARS-CoV-2 negative test with an HR of 0.98 (95% CI 0.96-0.99), indicating increased days of SARS-CoV-2 duration in older patients. Details are shown in Figure 4.

The multivariate logistic regression model also showed a significant difference in severe case conversion with an OR of 0.25 (95% CI 0.08-0.71) in patients who started Paxlovid treatment within five days of symptoms onset. Older age was associated with an increased risk of severe case conversion with an OR of 1.11 (95% CI 1.04-1.18). Details are shown in Table 4.

Table 4. Multivariable Logistic Regression Model for Severe case conversion.

Variable	OR (95% CI)	*p*
Paxlovid (≤ 5 days)	0.25 (0.08 - 0.71)	0.012
Gender (Female)	0.973 (0.36 - 2.62)	0.957
Age	1.11 (1.04 - 1.18)	0.002
Clinical classification		
Mild	Reference	
Moderate	0.587 (0.10 - 4.92)	0.582
Laboratory indicators		
CRP (≤ 10 mg/L)	Reference	
CRP (> 10 mg/L)	1.63 (0.58 - 4.81)	0.360
WBC (< 3.5 × 10^3/μL)	0.33 (0.02 - 2.52)	0.345
WBC (3.5-9.5 × 10^3/μL)	Reference	
WBC (> 9.5 × 10^3/μL)	2.12 (0.40 - 9.30)	0.258
IL-6 (≤ 6.6 pg/mL)	Reference	
IL-6 (> 6.6 pg/mL)	2.64 (0.65-14.4)	0.208
Comorbidities		
Diabetes	1.70 (0.50 - 5.57)	0.384
Hypertension	0.391 (0.14 - 1.04)	0.064
Cardiovascular disease	1.40 (0.50 - 3.86)	0.512
Chronic lung disease	2.56 (0.80 - 8.08)	0.108
Neurological disease	1.69 (0.62 - 4.65)	0.305
Malignancy	1.38 (0.26 - 5.83)	0.678
COVID-19 vaccination	0.90 (0.12 - 4.03)	0.901

Discussion

This retrospective study analyzed the differences in length of stay and SARS-CoV-2 duration among older

Figure 3. Multivariable Cox Regression Model for discharge from hospital.

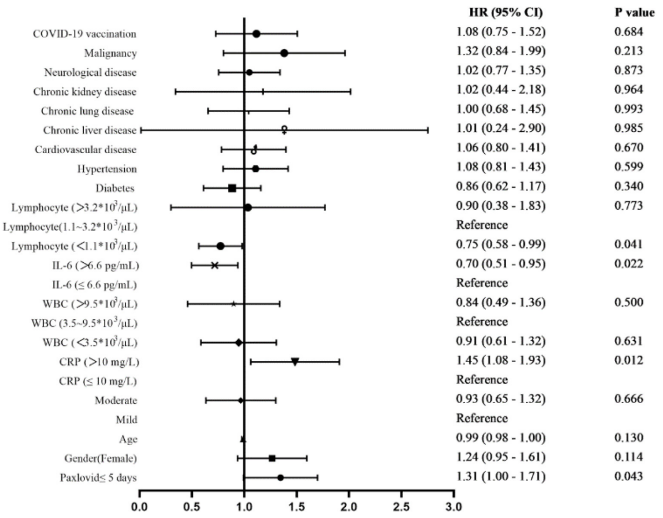
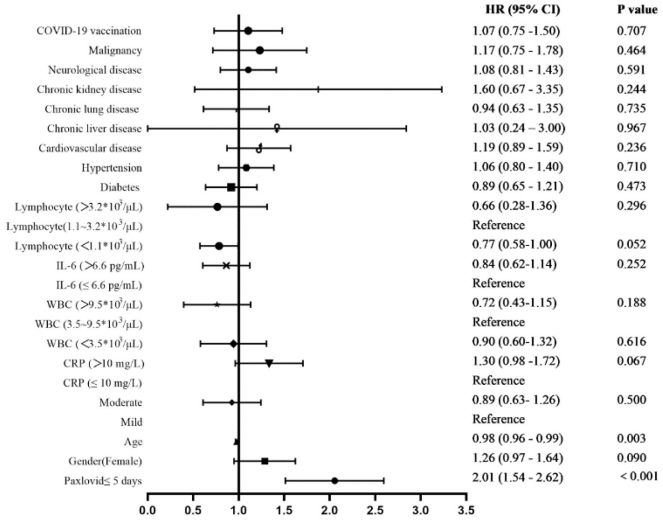


Figure 4. Multivariable Cox Regression Model for SARS-CoV-2 negative test.



COVID-19 patients treated with Paxlovid within or after five days of COVID diagnosis with symptoms onset. Severe case conversion was also compared between the two groups. In older adults with confirmed COVID-19, taking Paxlovid within five days reduced the length of stay and duration of SARS-CoV-2 in the respiratory tract of the patients compared to whom taking Paxlovid after five days of symptoms onset. However, among patients with mild COVID-19, no significant differences were observed in severe case conversion between the two groups.

Older patients are often associated with higher rates of diabetes, hypertension, coronary artery disease, and chronic obstructive pulmonary disease, all of which are important risk factors for COVID-19 [15]. Analyzing the use of Paxlovid in older patients can provide a theoretical basis for guiding the clinical rational drug use. The instruction of Paxlovid recommends initiating Paxlovid treatment as soon as possible within 5 days after the onset of COVID-19 symptoms. While the effect of initiating Paxlovid treatment after 5 days of symptoms onset has rarely been investigated. In this study, older patients were divided into EP group (within five days) and the LP group (after five days) based on the timing of initiating Paxlovid treatment post symptoms onset. The univariate analysis showed that the average length of stay was reduced by about two days for older patients who started Paxlovid treatment within five days compared to those who started Paxlovid treatment after five days. In line with WHO recommendations and China National Health Commission on the diagnosis and treatment of COVID-19, two consecutive negative SARS-CoV-2 nucleic acid testing of RT-PCR was used to determine SARS-CoV-2 negativity in patients. The duration of SARS-CoV-2 was shortened by about four days in the EP group. Significantly fewer patients with moderate COVID-19 progressed to severe cases conversion when starting Paxlovid treatment within five days. However, severe case conversion in patients with mild severity between the two groups showed no significant difference. The multivariate regression model showed that in addition to starting Paxlovid treatment after five days of COVID-19 diagnosis, older age in elderly patients was an independent risk factor for both the prolonged duration of SARS-CoV-2 and serve case conversion. Additionally, abnormal IL-6 levels and lower lymphocyte count indicate increased length of stay in elderly COVID-19 patients.

Paxlovid has been reported to significantly reduce hospitalization and mortality in patients with mild or moderate severities of COVID-19, as well as SARS-CoV-2 viral load [12,16]. A case of COVID-19 during long-term treatment (20 days) of Paxlovid has also been reported, suggesting that prolonging the therapeutic course of Paxlovid might be a feasible and safe strategy for severe COVID-19 patients [17]. Therefore, in this retrospective study, doctors may also extend the course of Paxlovid with an average course of 5.7 days based on the patient's condition and SARS-CoV-2 viral load. Among our study cohort, the SARS-CoV-2 variant was Omicron BA.2 with severe case conversion accounting for 15.6%. This finding was in accordance with the report that the Omicron BA.2 variant resulted in a lower incidence of severe cases [18,19]. In contrast to the EPIC-HR trial, which excluded patients expected to require hospitalization within 48 hours after randomization, this study retrospectively analyzed hospitalized patients (≥ 60 years old) with COVID-19, including mildly and moderately ill individuals. The subgroup analysis showed that mild and moderate COVID-19 patients in the EP group had shorter lengths of stay and SARS-CoV-2 duration compared to those in the LP group. However, the severe case conversion among mild COVID-19 patients had no significance between the two groups, indicating that Paxlovid might be equally effective in preventing severe case conversion whether received within 5 days or after 5 days of symptoms onset.

This study has the following limitations: 1) this is a single-center retrospective study, 2) delayed hospitalizations might lead to the delayed treatment of Paxlovid, and 3) the study population was older Chinese patients, and the results may not apply to other populations.

Conclusions

Starting Paxlovid within five days after symptoms onset of COVID-19 reduced the length of stay and SARS-CoV-2 virus duration in mild and moderately ill older adults. Starting Paxlovid therapy within five days could also reduce the severe case conversion in moderately COVID-19 patients. While the effect of Paxlovid on severe case conversion among mild COVID-19 patients might be comparable whether Paxlovid was administered within or after five days of a confirmed diagnosis of COVID-19 with symptoms onset.

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Corresponding authors

Jiao Yang
Deputy Chief Pharmacist
600 Yishan Road,
Shanghai 200233, China
Tel: +86-21-38297594
Email: yangjiaolily@126.com

Cheng Guo
Chief Pharmacist
600 Yishan Road,
Shanghai 200233, China
Tel: +86-21-64369181
Email: guopharm@126.com

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