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Coronavirus Pandemic

Association between Paxlovid and mortality in severe COVID-19 patients: a retrospective cohort study

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Abstract

Introduction: With limited research on the clinical effectiveness of Paxlovid for hospitalized patients with severe COVID-19, this study aims to assess its impact on clinical outcomes, providing essential insights for patient care.

Methodology: We collected consecutive data from SARS-CoV-2-infected patients at four hospitals between December 2022 and July 2023. We compared patient characteristics, clinical parameters, and treatment regimens between the Paxlovid and control groups. Analyses included crude, multivariable, doubly robust, and propensity score methods to evaluate Paxlovid's impact on 28-day mortality and to identify subgroup interactions.

Results: Of 574 patients treated with Paxlovid, 10.3% died within 28 days, versus 29.9% of 645 untreated patients. Unadjusted analysis showed a significant Paxlovid-associated reduction in 28-day mortality (OR 0.268, 95% CI 0.195-0.369; $p < 0.001$), sustained after adjustment (adjusted OR 0.298, 95% CI 0.198-0.447; $p < 0.001$). Paxlovid significantly decreased mortality in patients with infection durations ≤ 5 days (OR 0.401, 95% CI 0.227-0.707, $p < 0.001$) and > 5 days (OR 0.540, 95% CI 0.309-0.946, $p < 0.001$). Hospital stays were longer with Paxlovid (median 11 vs. 10 days, $p = 0.001$), with no significant effect on ICU admission rates.

Conclusions: Our findings suggest that Paxlovid significantly reduces 28-day mortality in severe COVID-19 patients, irrespective of infection duration over 5 days.

Key words: Paxlovid; COVID-19; severe; mortality.

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Introduction

The COVID-19 pandemic, now in its fifth year, has transitioned into an endemic-epidemic phase but continues to pose a significant threat to global health, economy, and social stability [1]. It has evolved significantly, from the original strain to Omicron subvariants such as XEC, KP.3.1.1, and JN.1, which exhibit enhanced immune evasion and transmissibility [2-4]. Despite a decline in COVID-19 overall prevalence, seasonal surges and localized outbreaks driven by emerging subvariants are expected to occur, consistent with an endemic-epidemic pattern [4,5]. A range of therapeutic measures have been proposed to treat SARS-CoV-2 infection [6-8]. Yet, 28-day mortality remains as high as 20–30% in severe or critically ill patients, particularly among those with advanced age, diabetes, cardiovascular disease, or low oxygenation index (PaO_2/FiO_2 < 200 mmHg) [4]. Moreover, the ongoing emergence of new SARS-CoV-2 variants, coupled with waning vaccine effectiveness over time, underscores the urgent need for novel, highly effective antiviral treatments with broad variant coverage, particularly in vaccinated but high-risk populations [5,9].

Paxlovid (nirmatrelvir/ritonavir) is an oral protease-inhibitor combination that has demonstrated efficacy in outpatients with mild-to-moderate COVID-19 [10], and remains one of the few oral antivirals available;

alternative agents such as remdesivir or monoclonal antibodies require intravenous infusion. While Paxlovid is currently FDA-approved only for outpatient use in high-risk individuals not requiring oxygen, its off-label use in hospitalized patients with severe COVID-19, including those on supplemental oxygen, has been increasingly reported in real-world settings. This study evaluates Paxlovid's role in reducing mortality in such patients.

Studies have consistently shown that nirmatrelvir significantly alleviates symptoms and reduces hospitalization and mortality in non-hospitalized patients with mild to moderate COVID-19 [11-13]. Furthermore, a small retrospective study by Yang *et al.* suggests that Paxlovid may reduce mortality in critically ill patients requiring mechanical ventilation, though this evidence is preliminary and lacks statistical power [14].

Despite these findings, there remains a significant gap in high-quality evidence—particularly from randomized controlled trials or large real-world cohorts—on the efficacy and safety of Paxlovid in hospitalized patients with severe COVID-19, especially those receiving oxygen or ICU-level care. This study aims to address that gap by assessing the real-world effectiveness of Paxlovid in reducing mortality among hospitalized patients with severe COVID-19.

Methodology

Study design and patients

We conducted a retrospective, multicentre cohort study at four hospitals in Chongqing from December 1, 2022, to July 30, 2023. Our study included hospitalized patients who met the following criteria: 1) tested positive for SARS-CoV-2 infection by real-time reverse transcription-polymerase chain reaction (RT-PCR), and 2) had a severe clinical classification upon admission. The severity of COVID-19 in this study was assessed according to the Chinese Diagnosis and Treatment Protocol for COVID-19 (Trial Version 10), which aligns with the definitions provided by the World Health Organization [15]. Severe cases were specifically defined as having a respiratory rate of 30 or more, oxygen saturation of 93% or less, a PaO_2/FiO_2 ratio of 300 mmHg or lower, or lung infiltrates exceeding 50%. Exclusion criteria included patients under 18 years of age, individuals with a clinical classification other than severe COVID-19 at admission, and those who lacked relevant patient data and clinical records.

Baseline covariates

The analysis included several covariates that have been identified in previous studies as potential factors contributing to mortality. These covariates included demographic factors such as age and gender, as well as comorbidities like diabetes, cardiovascular disease, chronic obstructive pulmonary disease, renal failure, liver disease, pulmonary tuberculosis, and current smoking status. Various laboratory test parameters were collected, including peripheral neutrophil count, absolute lymphocyte count, platelet count, as well as levels of C-reactive protein, procalcitonin, and D-dimer. Additionally, data regarding the utilization of invasive ventilation, antibiotics, glucocorticoids, Azvudine, and Tocilizumab were also collected. Considering the COVID-19 vaccination coverage surpassing 92.9% across the entire population in China [16], the inclusion of the vaccination status was consequently omitted due to the unavailability of individual-level vaccine type, dosing, or timing data.

Outcome measures

The study's primary endpoint focused on the 28-day mortality rate, which was calculated from the date of admission. Mortality data for discharged patients were collected through follow-up phone calls. Secondary outcomes included the length of hospital stay and the rate of ICU admissions during the initial hospitalization. Hospital stay duration was defined as the interval between admission and discharge, with adjustments made for patients who died during their hospitalization.

Subgroup analysis

To explore potential interactions within pre-specified subgroups, subgroup analyses were conducted for the primary outcome. Patients were categorized into two groups based on the duration from symptom onset to admission (0-5 days and > 5 days). We considered the time from symptom onset to admission as the duration of infection. This approach was adopted to emphasize the impact of the "duration of infection" on subgrouping and to minimize potential bias when comparing the duration of infection among patients with different illness durations. Furthermore, additional subgroups were defined based on other pre-specified factors. Subsequently, regression models were applied to estimate the odds ratios and their corresponding 95% confidence intervals, incorporating an interaction term between treatment assignment and the relevant subgroups.

Ethics statement

The study was conducted in accordance with the principles of the Declaration of Helsinki and received approval from the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (No. K2024-040-01). All procedures were conducted in compliance with local legislation and institutional protocols. Due to the retrospective nature of the study, the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University waived the need to obtain informed consent.

Statistical analysis

The study population was stratified into the Paxlovid (intervention) and no Paxlovid (control) groups based on their Paxlovid treatment status. Categorical variables were presented as counts and percentages, while continuous variables were described using mean (standard deviation) or median (interquartile range). Differences in categorical covariates were assessed using the chi-square test, and for continuous variables that did not follow a normal distribution, the Mann-Whitney U test was utilized. In addition, standard-of-care treatments—including antibiotics, systemic glucocorticoids, and invasive ventilation—were recorded as categorical variables (used vs. not used) and compared between groups.

To address potential biases, inverse probability weighted (IPW) models were employed to establish weighted cohorts, leveraging estimated propensity scores as weights. Logistic regression was performed on the weighted cohort to address imbalanced variables in the propensity score model. Additionally, a doubly robust model adjusting for all covariates was applied to ensure consistent and unbiased estimates.

Furthermore, a 1:1 ratio propensity score matching (PSM) approach was adopted to mitigate confounding factors and address group differences. Matching was performed without replacement based on the generated propensity scores, with a specified calliper value of 0.1. To assess the balance of baseline covariates between groups, both before and after propensity score matching, the standardized mean difference (SMD) was utilized. A covariate imbalance was indicated by an SMD greater than 0.1. Finally, the interaction between Paxlovid and selected baseline characteristics was assessed, and missing data were addressed through multiple imputations. A statistically significant outcome was determined by observing a p below 0.05.

Table 1. Comparison of baseline characteristics between the original cohort and the matched Cohort.

Variables	Original cohort			Matched cohort		
	Paxlovid (574)	Control (645)	SMD	Paxlovid (393)	Control (393)	SMD
Age [mean (SD)], years	72.9 (15.3)	74.4 (13.7)	-0.096	72.7 (15.1)	72.7 (14.5)	-0.003
Gender, N (%)						
Male	255 (44.4)	285 (44.2)	0.005	172 (43.8)	178 (45.3)	-0.031
Female	319 (55.6)	360 (55.8)	-0.005	221 (56.2)	215 (54.7)	0.031
Time* [mean (SD)], days	7.1 (6.0)	8.1 (6.4)	-0.172	7.3 (6.3)	7.6 (5.6)	-0.039
Calculated PaO2:FiO2 [mean (SD)]	283.0 (121.5)	262.9 (126.7)	0.165	280.6 (119.8)	277.8 (125.4)	0.023
Current smoking, N (%)	32 (5.6)	29 (4.5)	0.047	21 (5.3)	16 (4.1)	0.055
Laboratory findings						
Neutrophils × 10^9 [median (IQR)]	5.0 (3.3, 7.6)	6.0 (3.9, 9.2)	-0.340	5.1 (3.4, 8.0)	5.8 (3.8, 8.3)	-0.062
Lymphocytes × 10^9 [median (IQR)]	0.80 (0.50, 1.19)	0.75 (0.47, 1.17)	0.013	0.80 (0.49, 1.21)	0.77 (0.47, 1.18)	-0.033
Platelets × 10^9 [median (IQR)]	164 (119, 214)	176 (128, 228)	-0.124	168 (121, 224)	177 (129, 230)	-0.039
CRP [median (IQR)], mg/L	42.0 (12.5, 85.3)	42.5 (11.8, 100.5)	-0.117	38.9 (12.5, 84.6)	42.0 (14.8, 90.0)	-0.008
Procalcitonin [median (IQR)], ng/mL	0.10 (0.06, 0.28)	0.19 (0.08, 1.05)	-0.188	0.10 (0.06, 0.38)	0.14 (0.07, 0.59)	0.013
D-dimer [median (IQR)], mg/L	0.80 (0.43, 2.01)	1.21 (0.59, 3.61)	-0.295	0.84 (0.44 2.17)	1.02 (0.54 2.61)	-0.053
Systemic glucocorticoid, N (%)	444 (77.4)	358 (55.5)	0.522	267 (67.9)	270 (68.7)	-0.018
Dose of Glu# [median (IQR)], mg	40 (40, 80)	40 (40, 80)	0.296	40 (40, 80)	40 (40, 80)	-0.004
Duration of Glu [median (IQR)], days	8 (5, 13)	5 (3, 8)	0.449	6 (4, 9)	5 (3, 8)	0.048
Antibiotic agent, N (%)	445 (77.5)	443 (68.7)	0.212	280 (71.2)	283 (72.0)	-0.018
Azvudine, N (%)	25 (4.4)	61 (9.5)	-0.250	21 (5.3)	18 (4.6)	0.037
Tocilizumab, N (%)	28 (4.9)	7 (1.1)	0.176	5 (1.3)	7 (1.8)	-0.024
Invasive ventilation, N (%)	83 (14.5)	148 (22.9)	-0.241	72 (18.3)	69 (17.6)	0.022
Comorbidity, N (%)						
Diabetes	179 (31.2)	217 (33.6)	-0.053	123 (31.3)	126 (32.1)	-0.016
Cardiovascular disease	257 (44.8)	311 (48.2)	-0.069	181 (46.1)	183 (46.6)	-0.010
COPD	63 (11)	93 (14.4)	-0.110	53 (13.5)	53 (13.5)	0.000
Renal failure	62 (10.8)	104 (16.1)	-0.171	49 (12.5)	52 (13.2)	-0.025
Liver disease	94 (16.4)	49 (7.6)	0.237	38 (9.7)	41 (10.4)	-0.021
Pulmonary tuberculosis	8 (1.4)	8 (1.2)	0.013	6 (1.5)	6 (1.5)	0.000

IQR: interquartile range; N: number; SD: standard deviation; SMD: standardized mean difference; CRP: C-reactive protein; D: day; *: time from symptom onset to hospitalization; Glu: glucocorticoids; #: the dosage here refers to the dosage after conversion to methylprednisolone. A small number of patients using dexamethasone, prednisone or hydrocortisone would be uniformly converted to the dosage of methylprednisolone in this table (prednisone 5 mg ≈ methylprednisolone 4mg ≈ dexamethasone 0.75 mg ≈ hydrocortisone 20 mg).

Results

Study Population Characteristics

We consecutively collected data from 2084 hospitalized patients with confirmed SARS-CoV-2 infection between December 2022 and July 2023. After excluding 2 patients with incomplete clinical data, 853 patients who did not initially have severe COVID-19 upon admission, and 10 patients under the age of 18, resulting in a final cohort of 1219 patients. This cohort consisted of 574 patients who received treatment with Paxlovid (mean age: 72.9 years, 44.4% male), while the remaining 645 patients did not receive Paxlovid (mean age: 74.4 years, 44.2% male). The selection process of the study population is illustrated in Figure 1.

The cohort characteristics were summarized in Table 1. In general, patients in the Paxlovid group exhibited a shorter median time from symptom onset to hospitalization (7.1 ± 6.0 vs. 8.1 ± 6.4), suggesting earlier medical intervention in this group. They also presented with lower systemic inflammatory markers, including neutrophil count [5.0 (IQR 3.3-7.6) vs. 6.0 (IQR 3.9-9.2)], C-Reactive Protein (CRP) [42.0 (IQR 12.5-85.3) vs. 42.5 (IQR 11.8-100.5)], procalcitonin [0.10 (IQR 0.06-0.28) vs. 0.19 (IQR 0.08-1.05)], and D-dimer [0.80 (IQR 0.43-2.01) vs. 1.21 (IQR 0.59-3.61)], as well as higher oxygenation indices (PaO_2/FiO_2 ratio, herein referred to as P/F ratio: 283.0 ± 121.5 vs. 262.9 ± 126.7). These differences may reflect earlier disease recognition or selection bias toward less severe systemic involvement at baseline. Additionally, Paxlovid-treated patients had longer duration of systemic glucocorticoid therapy [8 (IQR 5-13) vs. 5 (IQR 3-8)], higher prevalence of concurrent liver disease (16.4% vs. 7.6%), lower rates of invasive mechanical ventilation (14.5% vs. 22.9%), and greater use of adjunctive therapies including Tocilizumab (4.9% vs. 1.1%), antibiotics (77.5% vs. 68.7%), and systemic glucocorticoids (77.4% vs. 55.5%). These differences suggest potential confounding by indication, as clinicians may have preferred Paxlovid in patients with more preserved organ function or lower disease severity, despite hospitalization. After matching, a total of 393 Paxlovid recipients and 393 matched controls were enrolled, ensuring balanced baseline features between the two groups with absolute standardized mean differences (SMD) lower than 0.1 (Supplementary Figure 1).

Figure 1. Identification of Paxlovid recipients and their matched controls among hospitalised patients with severe COVID-19.

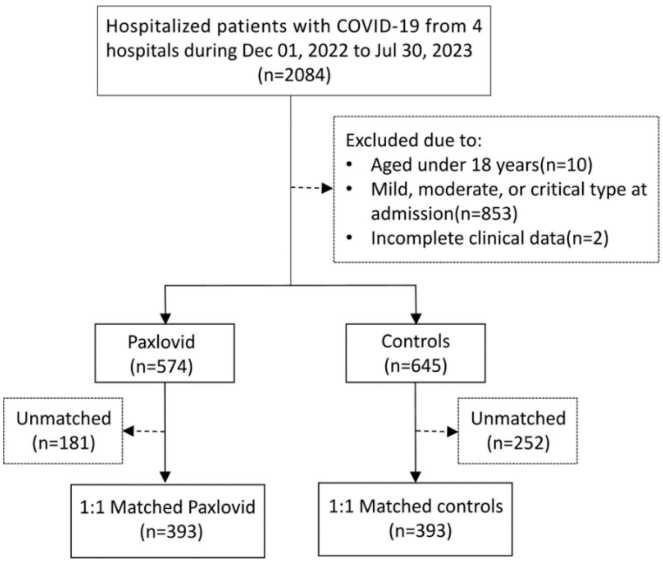
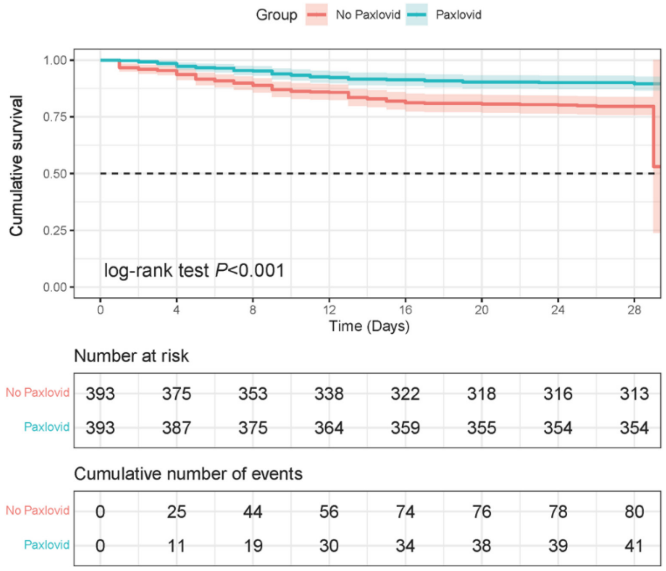


Figure 2. Kaplan-Meier plots the probability of death at each time point in the study.



Primary Outcome and Sensitivity Studies

Out of the 574 patients who received Paxlovid, 59 (10.3%) experienced mortality within 28 days, while among the 645 patients who did not receive Paxlovid, 193 (29.9%) passed away during the same period. The initial unadjusted analysis revealed a significantly favourable impact of Paxlovid on 28-day mortality in severe COVID-19 patients (OR 0.268, 95% CI 0.195-0.369; $p < 0.001$).

As shown in Figure 2, the survival curves for the Paxlovid and no Paxlovid groups diverge, indicating a significant difference in the probability of death over time. This visual representation supports the statistical findings and highlights the consistent beneficial effect of Paxlovid.

Following multivariable analysis, the adjusted odds

ratio was 0.298 (95% CI 0.198-0.447; $p < 0.001$), indicating a consistent beneficial effect. Furthermore, the doubly robust model accounting for all covariates also demonstrated a substantial impact on 28-day mortality (OR 0.222, 95% CI 0.181-0.264; $p < 0.001$). Additionally, the multivariable analysis utilizing inverse probability of treatment weighting (IPTW) based on the propensity score reaffirmed the notably beneficial effect of Paxlovid on 28-day mortality (OR 0.377, 95% CI 0.307-0.464; $p < 0.001$). Similarly, multivariable propensity-score analyses with matching produced comparable results, further supporting the favourable impact of Paxlovid on 28-day mortality (OR 0.298, 95% CI 0.176-0.503; $p < 0.001$) (Table 2).

An examination of the interaction between Paxlovid and predefined subgroups revealed that Paxlovid significantly reduces 28-day mortality not only in severe COVID-19 patients with infection duration 0-5 days (OR 0.401, 95% CI 0.227-0.707, $p < 0.001$), but also in those with infection duration exceeding 5 days (OR 0.540, 95% CI 0.309-0.946, $p < 0.001$). Furthermore, Paxlovid shows greater effectiveness in patients who are current smokers, antibiotic users, and those receiving invasive ventilation (p for interaction < 0.05 for all). However, the effectiveness of Paxlovid does not appear to be influenced by age, gender, the use of glucocorticoids, Azvudine, Tocilizumab, or comorbidities (p for interaction > 0.05 for all) in this study (Figure 3).

Secondary outcomes

We conducted an assessment of two secondary outcomes to explore the potential of Paxlovid in reducing the length of hospital stay and ICU admission rates. In the univariate analysis, it was observed that the Paxlovid group exhibited a significantly longer hospital stay compared to the control group (median, 11 vs. 10 days, $p = 0.001$) (Supplementary Figure 2A). This significance persisted in the multivariable logistic regression analysis (OR 1.027, 95% CI 1.009-1.045; $p = 0.004$) (Supplementary Figure 2B). There was no significant difference in ICU admission rates between the two groups ($p = 0.312$) (Supplementary Figure 2C).

Figure 3. The effectiveness of Paxlovid on 28-day mortality from all-cause in severe COVID-19 patients by subgroups of selected baseline characteristics. Odds ratios are plotted as squares; the horizontal lines represent 95% confidence intervals.

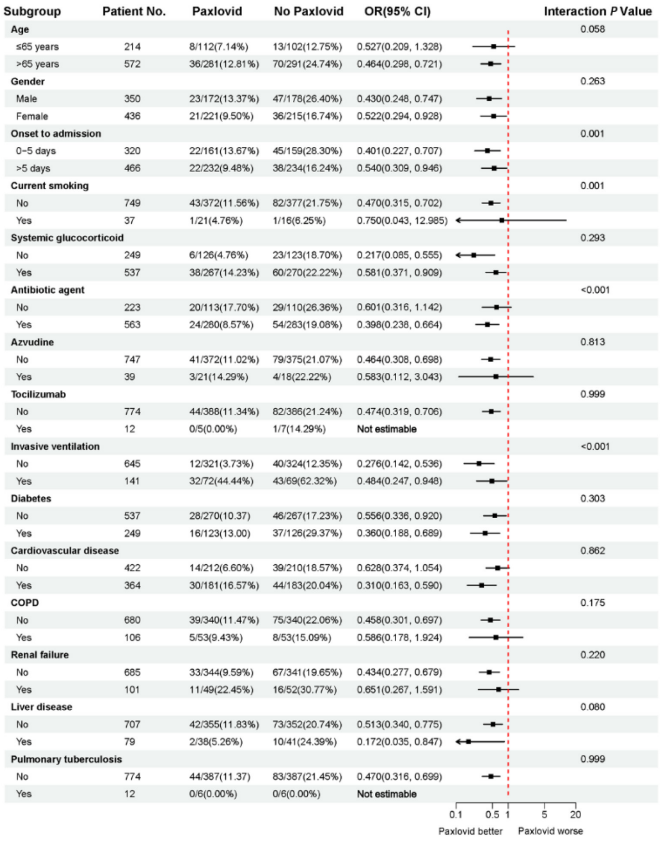


Table 2. Association of Paxlovid and 28-day mortality in COVID-19 patients by using in the crude analysis, multivariable analysis, doubly robust analysis, and propensity-score analyses.

Analysis	28-day mortality	*p*
No. of events/no. of patients at risk (%)		< 0.001
Paxlovid	59/574 (10.3)	-
No Paxlovid	193/645 (29.9)	-
Crude analysis - odds ratio (95% CI)	0.268 (0.195, 0.369)	< 0.001
Multivariable analysis - odds ratio (95% CI)*	0.298 (0.198, 0.447)	< 0.001
Doubly robust analysis - odds ratio (95% CI)#	0.222 (0.181, 0.264)	< 0.001
Propensity-score analyses - odds ratio (95% CI)		
With propensity score IPTW†	0.377 (0.307, 0.464)	< 0.001
With matching‡	0.298 (0.176, 0.503)	< 0.001

OR: odds ratio; CI: confidence interval; IPTW: inverse probability-of-treatment weighting; PSM: propensity score matching. * Shown is the odds ratio from the multivariable logistic regression model with additional adjustment for age, current smoking, past diagnoses, current medications and treatment, calculated PaO2:FiO2, and laboratory tests on presentation. # Shown is the odds ratio from the doubly robust model with the same covariates. The analysis included all 1219 patients; †Shown is the odds ratio from the multivariable logistic regression model with 28-day mortality as the binary response with the remained unbalanced covariates with inverse probability-of-treatment weighting according to the propensity score. The analysis included all the patients; ‡Shown is the odds ratio from a multivariable logistic regression model with identical covariates with matching according to the propensity score. The analysis included 786 patients (393 who received Paxlovid and 393 who did not).

Discussion

Our study demonstrates that Paxlovid significantly reduces 28-day mortality in hospitalised, hypoxemic patients with severe COVID-19, even when initiated more than five days after symptom onset. The median time to treatment in our cohort was seven days, underscoring the real-world feasibility and clinical value of mid-stage antiviral therapy in populations who frequently present late.

Our findings align with previous studies showing Paxlovid's mortality-reducing effects in patients with mild to moderate COVID-19, and also in critically ill patients [12,14,17-19]. Notably, we utilized a range of analytical methods to evaluate Paxlovid's impact on 28-day mortality rates, including unadjusted, multivariable, doubly robust modelling, propensity score weighting, and matching analyses. These consistent results affirm the stability and efficacy of Paxlovid, strongly endorsing its clinical use.

Importantly, while current FDA indications restrict Paxlovid to outpatient use in non-oxygen-requiring patients, our cohort exclusively comprised hospitalized severe cases meeting WHO criteria (including oxygen saturation $\leq 93\%$ or $PaO_2/FiO_2 \leq 300$ mmHg). The off-label administration observed in this study reflects real-world clinical scenarios where physicians may extend antiviral therapy to hypoxemic patients facing high mortality risk, particularly in resource-limited settings or during pandemic surges.

Studies suggest that early Paxlovid administration within five days of infection offers greater benefits, with an 88% reduction in the risk of death [13,17]. Additionally, subgroup analysis reveals that Paxlovid significantly lowers the 28-day mortality rate in severe COVID-19 patients, even when administered after five days. This underscores Paxlovid's sustained efficacy in severe COVID-19 cases, including advanced stages. Unfortunately, time to nasopharyngeal PCR negativity was not systematically recorded; incorporating serial viral-load data in future studies would clarify whether late-initiated Paxlovid accelerates virological clearance. Moreover, significant interaction effects were observed in current smokers and antibiotic users, suggesting potential influences on Paxlovid's therapeutic response. Enhanced benefit in antibiotic users may reflect viral-bacterial synergism or heightened inflammation; confirmation with prospectively defined bacterial co-infection markers is warranted. Conversely, factors like age, gender, glucocorticoid use, Azvudine, Tocilizumab, and comorbidities showed no significant effect on Paxlovid's effectiveness. No pharmacodynamic interaction was detected between Paxlovid and Azvudine; however, Azvudine was administered empirically to patients with prolonged viral shedding or clinical deterioration, creating inherent selection bias. Co-administration with ritonavir raises theoretical concerns (bone-marrow suppression, hepatotoxicity) and lacks safety data; combined use should be restricted to clinical trials until pharmacokinetic and outcome evidence emerge. Similarly, Wan *et al.* [18] found no significant interaction between Paxlovid treatment and factors such as age, gender, or Charlson Comorbidity Index. In contrast, Najjar-Debbiny *et al.* [10] reported interactions with Paxlovid treatment in the elderly, immunocompromised patients, and those with neurological or cardiovascular conditions. Collectively, these findings emphasize the importance of personalized treatment strategies and individual patient characteristics in Paxlovid therapy.

However, several important observations need to be considered. First, Paxlovid-treated patients had a significantly longer median hospital stay than the control group (11 vs 10 days; $p = 0.001$). This paradoxical prolongation likely reflects survival bias (i.e., patients who survived longer had more opportunities for discharge planning), heterogeneous institutional discharge policies, or closer monitoring of patients receiving off-label therapy, rather than a true harmful effect of Paxlovid. Notably, the small sample size may have limited the study's statistical power. Additionally, varying discharge criteria across hospitals could have influenced the hospital stay duration for those treated with Paxlovid. Moreover, disparities in ICU bed availability and admission protocols may explain the similar ICU admission rates between the groups. Consistent with previous research findings [13,20,21], we found no significant difference in ICU admission rates between the Paxlovid and control groups among hospitalized severe patients, suggesting that Paxlovid treatment did not significantly reduce the risk of subsequent ICU transfer in this already severely ill population.

Our findings provide preliminary evidence regarding the therapeutic efficacy of Paxlovid in severe COVID-19 patients. The results suggest that even in oxygen-dependent patients - a population excluded from current FDA labelling - Paxlovid may confer significant survival benefits. Nonetheless, the study has several limitations to consider. Firstly, the off-label use of Paxlovid in oxygen-requiring patients limits direct comparability with regulatory indications. Although this reflects real-world practice, future studies should stratify outcomes by oxygen support levels to refine

clinical guidance. Additionally, potential confounding factors inherent in retrospective studies could affect treatment outcomes. Lastly, our study did not assess the impact of COVID-19 vaccination status on patient outcomes. However, other studies suggest that Paxlovid's effectiveness is vaccination-independent [10,18]. Considering the potential impact of vaccination on COVID-19 disease, incorporating vaccination status in the study would offer a more thorough evaluation of the efficacy and safety of Paxlovid in real-world clinical practice.

Despite its limitations, our study provides strong evidence for Paxlovid's efficacy in severe COVID-19, evidenced by both IPTW and doubly robust models. Moreover, Paxlovid's efficacy was sustained in patients with infections lasting over 5 days. Importantly, early Paxlovid administration correlated with improved efficacy, underscoring the need for timely intervention in severe cases. As an oral regimen, Paxlovid is impractical in critically ill patients with altered mentation, ileus, or enteral feeding contraindications; we lacked granular data on respiratory-support modality (e.g., high-flow nasal oxygen, non-invasive or invasive ventilation). Future studies should evaluate the feasibility of enteral antiviral therapy across different respiratory-support levels and explore parenteral alternatives for patients unable to tolerate oral medications. Finally, no significant difference in ICU admission rates was observed between Paxlovid-treated and control groups. This suggests that Paxlovid use did not reduce the need for intensive care.

Conclusions

In summary, Paxlovid administration significantly reduced 28-day mortality in severe COVID-19 patients, even for those with extended infection durations over 5 days. This observation, derived from real-world off-label use, supports prospective randomised trials of Paxlovid in hospitalised, oxygen-requiring patients and highlights the need for antiviral options that remain feasible in critically ill or enteral-intolerant populations. It provides valuable guidance for medical practice and helpful insights for future clinical trials and practices.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

Mingjin Yang and Yanchao Liang initiated the study concept and were involved in the design and data analysis. Bin Liu contributed significantly to data collection and ensured its integrity throughout the research process. Mingjin Yang was instrumental in the statistical analysis and interpretation of the results. All authors collaborated in refining the manuscript, providing critical feedback at each stage, and have collectively approved the final version for publication.

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Conflict of interest

No conflict of interest is declared.

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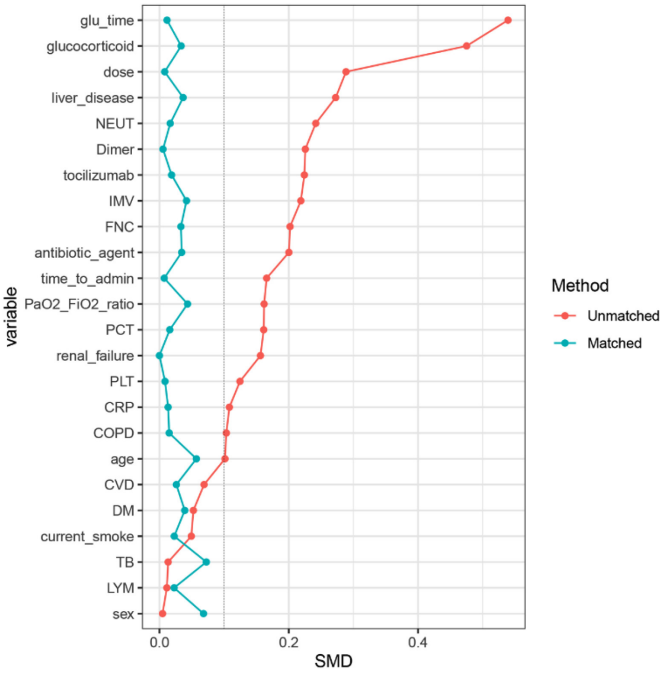
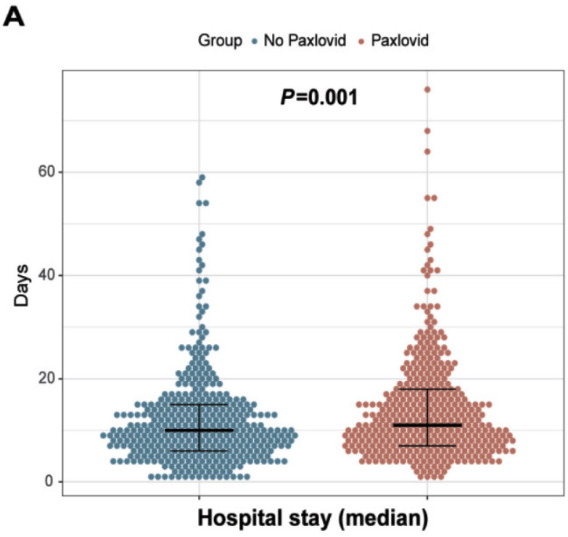
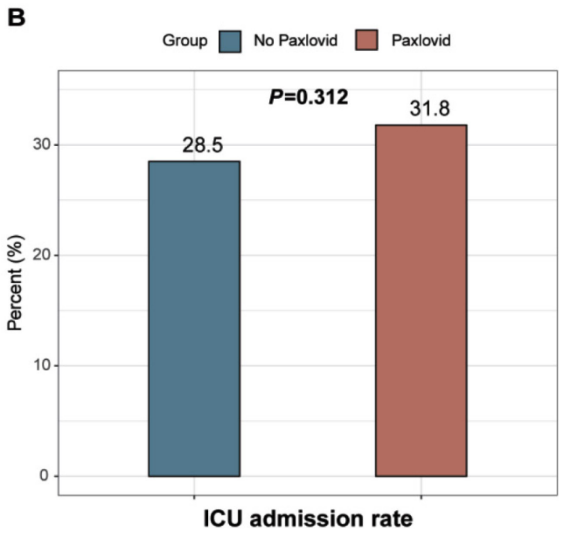
Annex – Supplementary Itema

Supplementary Figure 1. Standard mean differences between the groups before and after 1:1 propensity score-matching.



Supplementary Figure 2. Secondary outcomes. **A:** Median days of hospital stay by Paxlovid and control groups; **B:** Rate of ICU admission by Paxlovid and control groups (after propensity score matching); **C:** A multivariable logistic regression analysis assessed the relationship between Paxlovid usage and other variables, after propensity score matching and adjusting for baseline characteristics in the patients.





C

Characteristics	OR(95% CI)	*P* Value
Hospital stay	1.027(1.009, 1.045)	0.004
ICU admission (Reference: None)	1.173(0.775, 1.774)	0.450