ORIGINAL ARTICLE

Effectiveness of nirmatrelvir/ritonavir (Paxlovid®) in preventing hospitalisation and death among COVID-19 patients: a prospective cohort study

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ABSTRACT

Introduction: Previous trials and real-world studies have shown that nirmatrelvir/ritonavir (Paxlovid®) reduces hospitalisation and deaths in symptomatic, high-risk, non-severe COVID-19 patients. However, there was a scarcity of data on its effectiveness in the local setting. This study aimed to determine the effectiveness of Paxlovid® in reducing hospitalisation and mortality among COVID-19 patients and to identify the types of adverse events that occur after taking Paxlovid®.

Materials and Methods: A two-arm prospective cohort study was conducted among adult patients with COVID-19 categories 2 and 3 treated with Paxlovid® and a matched control group. A standard risk-stratified scoring system was used to establish Paxlovid® eligibility. All patients who were prescribed Paxlovid® and took at least one dose of Paxlovid® were included in the study. The control patients were selected from a centralised COVID-19 patient registry and matched based on age, gender and COVID-19 stage severity.

Results: A total of 552 subjects were included in the study and evenly allocated to the treatment and control groups. There was no statistically significant difference in 28-day hospitalisation after diagnosis [Paxlovid®: 26 (9.4%), Control: 34 (12.3%), OR: 0.74; 95%CI, 0.43-1.27; p=0.274] or all-cause death [Paxlovid®: 2 (0.7%), Control: 3 (1.1%), OR 1.51; 95%CI, 0.25-9.09; *p*=0.999]. There was no significant reduction in hospitalisation duration, intensive care unit admission events or supplementary oxygen requirement in the treatment arm. Ethnicity, COVID-19 severity at diagnosis, comorbidities and vaccination status were predictors of hospitalisation events.

Conclusion: In this two-arm study, Paxlovid® did not significantly lower the incidence of hospitalisation, all-cause death and the need for supplemental oxygen. Adverse effects were frequent but not severe. Paxlovid® efficacy varied across settings and populations, warranting further real-world investigations.

KEYWORDS:
effectiveness; nirmatrelvir/ritonavir; hospitalisation; death; COVID-19; real-world; Malaysia

INTRODUCTION

As of December 2022, the coronavirus disease 2019 (COVID-19) has killed 7.5 million people globally, with more than 650 million positive cases.[1] Between January 24 and February 7, 2022, the predominant COVID-19 variant in Malaysia was Omicron, accounting for 92% of cases, followed by Delta at 8%. On February 7, 2022, the Ministry of Health declared Omicron as the dominant strain in Malaysia.[2] As of June 1, 2022, Malaysia had reported 5.10 million confirmed COVID-19 cases and 37,087 deaths related to COVID-19.[3]

In April 2022, WHO recommended the use of Nirmatrelvir/Ritonavir (Paxlovid®) for high-risk patients with non-severe COVID-19 based on the available evidence from two randomised controlled trials (EPIC-SR and EPIC-HR).[4] Nirmatrelvir is a novel SARS-CoV-2 major protease inhibitor targeting SARS-CoV-2 3CL, while ritonavir is an HIV-1 protease inhibitor that inhibits the CYP3A-mediated metabolism of nirmatrelvir.[5]

Hammond et al. found that managing symptomatic Covid-19 with nirmatrelvir/ritonavir (Paxlovid®) reduced the risk of progression to severe Covid-19 by 89% compared to placebo, with no apparent safety issues.[6] Nirmatrelvir/ritonavir (Paxlovid®) significantly reduced death and hospitalisation in the 65 and older group, with adjusted hazard ratios of 0.21 (95% CI, 0.05 to 0.82) and 0.74 (95% CI, 0.35 to 1.58), respectively.[7]

In a large-scale retrospective observational cohort study of non-hospitalised adult patients infected with COVID-19, treatment with Paxlovid® was associated with a lower rate of 28-day all-cause hospitalisation and 28-day all-cause death compared to no antiviral treatment.[8] Another retrospective cohort study conducted in Hong Kong found that the use of Paxlovid® was associated with decreased risks of death, hospitalisation and in-hospital disease progression.[9]

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Despite a few studies demonstrating the effectiveness of Paxlovid® in real-world settings,[7-10] there remains a notable gap in the existing evidence, particularly in the South East Asia setting. This study provides insights regarding the use of Paxlovid® specifically for the Omicron variant, compared to studies with larger populations and considering the diverse ethnic populations found in countries like Malaysia.

This study aims to assess the effectiveness of Paxlovid® in reducing hospitalisations and death among COVID-19 patients and determine the occurrence of adverse events associated with its use.

MATERIALS AND METHODS

This prospective cohort study included adult patients with category 2 and category 3 COVID-19 who received treatment with Paxlovid® and a matched control group. The study was conducted across 24 study sites, comprising 13 hospitals and 11 District Health District Offices in the Perak state of Malaysia.

Paxlovid® Regimen

The recommended dose for patients with normal renal function (eGFR > 60ml/min) is 300 mg of nirmatrelvir (two 150 mg tablets) and 100 mg of ritonavir (one 100 mg tablet), taken orally twice daily for 5 days. Adjusted dosage for renal impaired (eGFR 30–60 ml/min) patients is nirmatrelvir 150 mg (1 tablet) and ritonavir 100 mg twice daily.

Paxlovid® Eligibility

A standard risk-stratified scoring system was used to prioritise Paxlovid® among patients with COVID-19. One point was given to each of the following characteristics: age ≥ 60 years, immunocompromised, presence of comorbidities, incomplete vaccination (did not complete booster dose or unvaccinated), obesity and radiographic abnormalities in chest X-ray. The scores were summed up and recorded in the Paxlovid® initiation criteria checklist. Patients who scored equal or more than 2 were eligible for Paxlovid®.

Patients were not eligible for Paxlovid® if they were less than 18 years old, asymptomatic (Category 1), with symptoms onset more than 5 days, started on oxygen, diagnosed liver disease (Child-Pugh Class C) or end-stage renal failure (eGFR <30 ml/min), pregnant or breastfeeding, with the inherent risk of hypersensitivity and taking interacting medications, including carbamazepine, phenobarbital, phenytoin, voriconazole, warfarin, rivaroxaban, colchicine, atazanavir, darunavir, rifampicin, quetiapine, amlodipine, felodipine, diltiazem, nifedipine, digoxin, lovastatin, simvastatin, atorvastatin, rosuvastatin, ethinyl oestradiol, cyclosporine, tacrolimus, sirolimus, salmeterol, methadone, sildenafil, dexamethasone and methylprednisolone.

Study Inclusion and Exclusion

We included all patients prescribed Paxlovid® in May and June 2022 who consumed at least one dose of Paxlovid®. We excluded those lost to follow-up (self-reported as having COVID-19 through the Malaysian contact-tracing mobile application MySejahtera but did not seek treatment at clinics or hospitals) and did not consume any dose of Paxlovid® after receiving the medication.

Matched Control

Patients not prescribed Paxlovid® in March and April 2022 were included in the control arm in a 1:1 ratio. Control patients could not be attained in the same period as the treatment group because all eligible patients were started with Paxlovid® from May onwards. The control patients were identified and retrieved from the state-centralised COVID-19 patients registry and matched using age, gender and pre-treatment COVID-19 stage severity.

Sample Size and Sampling Method

The sample size was calculated using G-Power (proportion difference from constant, binomial test, one sample case) sample size calculator. Based on Hammond et al. 2022, 0.7% of Paxlovid® patients were hospitalised until Day 28, compared to 6.5% of placebo patients who were hospitalised or died.[6] To detect a difference of 5.8% between the two arms, an alpha error of 0.05, a power of 99% and a minimum sample size of 117 were required. Assuming 30% incomplete data, each arm's final sample size was 167. Consecutive sampling was employed, where all cases which fulfilled the inclusion and exclusion criteria were sampled.

Outcome Measures

The primary effectiveness measure was an event of 28-day hospitalisation post-COVID-19 diagnosis. Paxlovid®-related adverse events and 28-day post-diagnosis death were the secondary outcome measures.

Data Collection

The data of patients who were prescribed Paxlovid® were entered into the state centralised Paxlovid® initiation registry, and eligible patients were identified through the registry. Data retrieved included patients' age, gender, ethnicity, COVID-19 category during the first encounter, types and severity of adverse events (Days 1 to 5 post-initiation), and the total doses ingested. We solicited patients' admission or readmission outcomes, oxygen requirement and adverse events (Days 6–28) through phone follow-up on Day 28 post-initiation.

Several sources of secondary data supplemented this: (i) Paxlovid® initiation criteria checklist containing comorbidities, obesity, immunocompromised status, dose prescribed, radiographic abnormalities in chest X-ray; (ii) Centralised COVID-19 vaccine database containing vaccination status and types of vaccines administered; (iii) National Registration Department, which provided the death data; (iv) electronic hospital information system containing the admission duration, oxygen requirement and intensive care unit (ICU) admission status.

Control group data retrieved included patients' age, gender, ethnicity and COVID-19 severity category during the first encounter from the state-centralised COVID-19 patients registry and supplemented with data from the Centralised COVID-19 vaccine database, National Registration Department and hospital information system.

Data Analysis

The demographic characteristics of the patients in both the treatment and control arm were descriptively analysed. Events and duration of hospitalisation, ICU admission,

Table I: Characteristics of patients who received Paxlovid® and matched population controls (n=552)

	Paxlovid® group (n = 276)	Control group (n = 276)	*p* value
Age, median (IQR)	53 (40-66)	53 (40-63)	0.242[a]
Gender, n (%)			
Male	134 (48.6)	128 (46.4)	0.282
Female	142 (51.4)	148 (53.6)	
Ethnicity, n (%)			
Malay	157 (56.9)	171 (62.0)	0.189
Chinese	66 (22.5)	61 (22.1)	
Indian	51 (18.5)	43 (15.6)	
Others	6 (2.2)	1 (0.4)	
Covid severity at (before treatment), n (%)			
2A	258 (93.5)	258 (93.5)	0.999
2B	10 (3.6)	10 (3.6)	
3	8 (2.9)	8 (2.9)	
Comorbidities, n (%)			
Hypertension	149 (54.0)	160 (58.0)	0.346
Diabetes	90 (32.6)	101 (36.6)	0.325
Dyslipidaemia	8 (2.9)	20 (7.2)	0.020
Chronic kidney disease	6 (2.2)	11 (4.0)	0.218
Respiratory disease	24 (8.7)	26 (9.4)	0.767
Cancer	6 (2.2)	2 (0.7)	0.154
Cardiovascular disease	29 (10.5)	32 (11.6)	0.684
Others	13 (4.7)	32 (11.6)	0.003
COVID-19 vaccination status, n (%)			0.237
Completed booster dose	202 (73.5)	186 (67.4)	0.119
Completed primary doses	67 (24.4)	85 (30.8)	0.091
Unvaccinated	6 (2.2)	5 (1.8)	0.756
Adherence, n (%)			
Completed regimen (10 doses)	259 (93.8)		
Taken at least one dose	17 (6.2)		

[a] Mann-Whitney U test performed
[b] Reason of non-adherence: intolerable adverse events (n=9), patient refusal (n=5), progression to severe COVID-19 (n=1), others (n=2).

Table II: Comparison of hospitalisation, ICU admissions, oxygen requirement and all-cause death outcomes between Paxlovid® recipients and matched controls (n=552)

	Overall (n=552)	Control (n=276)	Paxlovid® (n=276)	Odds ratio (95%CI)	p-value
Hospitalisation, n (%)	60 (10.9)	34 (12.3)	26 (9.4)	0.74 (0.43–1.27)	0.274[a]
Duration of hospitalisation in days, median (IQR)	4.0 (2–6)	4.0 (2–7)	5.0 (3–6)	-	0.952[b]
ICU admission, n (%)	5 (8.3)	3 (8.8)	2 (7.7)	1.51 (0.25–9.09)	0.999[c]
Supplemental oxygen requirement, N (%)	13(21.7)	10 (29.0)	3(11.5)	3.41 (0.93–12.52)	0.05[a]
All-cause death, n (%)	5 (0.9)	3 (1.1)	2 (0.7)	1.51 (0.25–9.09)	0.999[c]

[a]Chi-square test.
[b]Mann–Whitney U test.
[c]Fisher's exact test.

supplemental oxygen requirement and all-cause death outcomes for Paxlovid® recipients were compared with matched controls using the Chi-square (χ^2) statistic and Fisher's exact test for categorical variables and the Mann–Whitney U test for continuous variables. Multiple logistic regression analysis was performed to determine the independent predictors of hospital admissions and death. The model was constructed consisting of variables significant at the 0.25 level. Inferential data were expressed in odd ratios and 95% confidence intervals, and a p-value of 0.05 indicates statistical significance.

Ethics Approval

This study was registered in the National Medical Research Registry (NMRR ID-22-01372-NIL) and approved by Medical Research Ethical Committee [22-01372-NIL(1)]. Consent was obtained from the treatment group patients during the first encounter regarding the 28-day phone call follow-up.

RESULTS

Baseline Patient Characteristics

552 subjects were evenly divided into both arms and analysed. Of 276 patients who received Paxlovid® treatment, the median age was 53 years (IQR: 40-66 years); 142 (51.4%) were women, and 157 (56.9%) were Malay individuals. The most common comorbidities were hypertension (54.0%) and diabetes (32.6%). The baseline demographic and clinical characteristics were generally similar in both arms. Of those who received Paxlovid®, 259 (93.8%) completed the 5-day

Table III: Univariate and multivariate binary logistic regression for day 28 post-diagnosis hospitalisation event (n=552)

Variable	Crude OR (95% CI)	*p* value	Adjusted OR (95%CI)	*p* value
Age (year)	1.01 (1.00–1.03)	0.129		
Gender				
Female	1.21 (0.70–2.07)	0.50		
Male	1.00			
Ethnicity				
Non-Malay	2.08 (1.21–3.57)	0.008	2.04 (1.10–3.80)	0.024
Malay	1.00		1.00	
Severity of COVID-19 at diagnosis		<0.001		<0.001
2a	0.02 (0.01–0.07)	<0.001	0.03 (0.01–0.10)	<0.001
2b	0.12 (0.03–0.59)	0.009	0.13 (0.02–0.69)	0.016
3	1.00		1.00	
Hypertension				
Yes	1.11 (0.65–1.92)	0.697		
No	1.00			
DM				
Yes	0.94 (0.53–1.66)	0.827		
No	1.00			
Dyslipidaemia				
Yes	1.85 (0.68–5.07)	0.229		
No	1.00			
CKD				
Yes	2.63 (0.83–8.35)	0.10		
No	1.00			
Respiratory				
Yes	3.40 (1.69–6.85)	<0.001	0.40 (0.18–0.93)	0.032
No	1.00		1.00	
Cancer				
Yes	2.79 (0.55–14.2)	0.215		
No	1.00			
CVS				
Yes	2.26 (1.13–4.54)	0.022	0.43 (0.20–0.95)	0.036
No	1.00		1.00	
Others				
Yes	1.89 (0.84–4.28)	0.126		
No	1.00			
Vaccination status		0.004		0.015
Unvaccinated	6.15 (1.71–22.1)	0.005	6.33 (1.39–28.82)	0.017
Complete primary	1.92 (1.09–3.39)	0.025	1.97 (1.00–3.88)	0.049
Complete booster	1.00		1.00	
Paxlovid®				
No	1.35 (0.79–2.32)	0.275		
Yes	1.00			

Backward LR method was applied; No multicollinearity and no interaction; Hosmer Lemeshow test, p value=0.506; Classification table 90.9% correctly classified; area under receiver operating characteristics (ROC) curve was 78%. OR: Odd ratios; DM: Diabetes mellitus; CKD: Chronic kidney disease; CVS: Cardiovascular disease

course treatment. Overall, 73.5% of the patients had received a booster dose, 24.4% received the primary series, and 2.2% were unvaccinated (Table I).

Hospitalisation, ICU Admission, Oxygen Requirement and All-Cause Death

From the first day of diagnosis to day 28 post-diagnosis, 60 (10.9%) patients required hospitalisation. There were no statistically significant differences in day 28 post-diagnosis hospitalisation events between the two arms [Paxlovid®: 26 (9.4%), Control: 34 (12.3%), OR: 0.74; 95% confidence intervals, 0.43–1.27; *p*=0.274]. The median duration of hospitalisation was 4.0 days (IQR: 2–6 days). There were no significant differences in total ICU admissions and supplemental oxygen requirement in the treatment arm. Five deaths were reported at day 28 post-diagnosis, with no significant differences across both arms [Paxlovid®: 2 (0.7%), Control: 3 (1.1%), OR: 1.51; 95%CI 0.25-9.09; *p*=0.999] (Table II).

Predictive Factors of Hospitalisation

Non-Malays had 2.04 times greater odds of hospitalisation than Malays. [OR: 2.04; 95%CI 1.10–3.80; *p*=0.024]. Ironically, patients with underlying respiratory [OR: 0.40; 95%CI, 0.18–0.93; *p*=0.032] and cardiovascular disease [OR: 0.43; 95%CI, 0.20–0.95; *p*=0.036] demonstrated lower risks of hospitalisation.

The odds of hospitalisation for COVID-19 varied based on the status of vaccination. Patients vaccinated with the primary series without a booster dose were more likely to be hospitalised than boosted patients [OR 1.97; 95%CI 1.00–3.88; *p*=0.049]. The odds of hospitalisation were 6.3 times higher in unvaccinated patients compared to those who were boosted [OR: 6.33; 95%CI, 1.39–28.82; *p*=0.017].

A milder stage of COVID-19 at diagnosis was associated with decreased odds of hospitalisation. Patients who were diagnosed with Stage 2a [OR: 0.03; 95%CI, 0.01–0.10; *p*<0.001] and Stage 2b [OR: 0.13; 95%CI, 0.02–0.69; *p*=0.016]

Supplementary Table I: Demographic and clinical characteristics of the hospitalised patients (n = 60)

	Control group (n=34)	Paxlovid® group (n=26)	*p* value
Age, median (IQR)	55.5 (33.3–72.3)	58.5 (36.8–69.3)	0.715[a]
Gender, n (%)			
Male	13 (38.2)	13 (50.0)	0.362
Female	21 (61.8)	13 (50.0)	
Ethnicity, n (%)			
Malay	13 (38.2)	13 (50.0)	0.631
Chinese	14 (41.2)	8 (30.8)	
Indian	7 (20.6)	5 (19.2)	
Others			
Covid severity at (before treatment), n (%)			
2A	25 (73.5)	15 (57.7)	0.282[b]
2B	2 (5.9)	5 (19.2)	
3	7 (20.6)	6 (23.1)	
Comorbidities, n (%)			
Hypertension	19 (55.9)	16 (61.5)	0.66
Diabetes	10 (29.4)	10 (38.5)	0.582
Dyslipidaemia	4 (11.8)	1 (3.8)	0.377[b]
Chronic kidney disease	2 (5.9)	2 (7.7)	0.999[b]
Respiratory disease	8 (23.5)	5 (19.2)	0.76
Cancer	1 (2.9)	1 (3.8)	0.999[b]
Cardiovascular disease	6 (17.6)	6 (23.1)	0.747
Others	6 (17.6)	2 (7.7)	0.446[b]
COVID-19 vaccination status, n (%)			
Completed booster dose	18(52.9)	15(57.7)	0.92[b]
Completed primary doses	14(41.2)	9(34.6)	
Unvaccinated	2(5.9)	2(7.7)	
Adherence, n (%)			
Completed regimen (10 doses)		22 (84.6)	
Taken at least one dose		4(15.4)	

[a]Mann–Whitney U test was performed.
[b]Fisher's exact test was performed.

were associated with a lower risk of hospitalisation compared to stage 3 (Table III).

Adverse Events

The reported adverse events after Paxlovid® ingestion was as follows: dysgeusia (96, 61.1%), diarrhoea (49, 31.2%), nausea and vomiting (11, 7.0%), myalgia (7, 4.5%), abdominal pain (5, 3.2%), hypertension (3,1.9%) and others (41, 26.1%). There was no life-threatening adverse event reported.

DISCUSSION

This was a real-world study in a multiracial country within the ASEAN region to evaluate the effectiveness of Paxlovid® in reducing hospitalisation and all-cause death. Our study found hospitalisation and all-cause death occurred in 9% and 0.8% of Paxlovid® patients, respectively, which was higher than what was reported by previous studies.[6,11,12] Hammond et al. reported 0.77% of hospitalisation with no death,6 while Shah et al. reported 0.47% of hospitalisation and 0.01% of death in patients receiving Paxlovid®.[11] Furthermore, Malden and colleagues discovered that emergency department visits or hospitalisations were less than 1% in the 5–15 days following Paxlovid® treatment.[12] Similarly, larger real-world cohort studies[7-10] carried out during Omicron domination reported a reduction of hospitalisation and death in the Paxlovid® group, but with a lower magnitude than Hammond et al. In contrast with previous studies, we did not find a significant reduction in hospitalisation and all-cause death in patients who took Paxlovid®. Also, we did not observe any significant reduction in intensive care unit (ICU) admission and supplemental oxygen requirement among patients taking Paxlovid®. Although previous studies did not find a reduction in ICU admission among patients who took Paxlovid®, a significantly lower need for oxygen therapy was reported.[9,10] The insignificant results might be explained by several differences between the studies, including the study population and settings.

First, the population's natural immunity may have risen over time due to previous strain infections, contributing to lower severity, hospitalisation and death.[13] Second, about 7% of our study population did not adhere to the Paxlovid® regimen, which may reduce the effectiveness of Paxlovid®.[10]

Notably, the EPIC-HR trial6 included only unvaccinated patients, whereas our study included merely 2% unvaccinated subjects, and 70% had received the booster dose. Similarly, two previous studies found no significant reduction in hospitalisation or all-cause death among vaccinated inpatients who received Paxlovid®.[9,14] The action of Paxlovid® could be masked by COVID-19 vaccinations, which effectively reduce disease severity and death.[10,15] Hence, our findings may rationalise the prioritisation of Paxlovid® among unvaccinated patients, especially in resource-poor

settings. Lastly, the fact that we included fewer subjects in the over-65 age group in which Paxlovid® was found to be more efficacious[7] may have contributed to the underestimation of its efficacy.

Our analysis showed non-Malays had higher hospitalisation odds than Malays, suggesting the potential association between ethnicity and COVID-19 severity.[10,16,17] It is important to note that genetic polymorphisms may affect drug metabolism and medication response.[18] Variations in allelic frequencies of the CYP2D6*10 gene have been observed among the Chinese, Malay and Indian populations.[19] Apart from different drug metabolism profiles, ethnicity could be the surrogate for underlying factors, including socioeconomic status, exposure to virus-related- environments and access to health care.[20] Further investigation is needed in this area to reduce health inequalities across different ethnic groups.[17]

The most commonly reported Paxlovid®-related adverse events in this study were dysgeusia, diarrhoea, and vomiting, which mirrored previous findings.[6,14] While the reported adverse events were not severe, they might lead to patients' non-adherence, causing drug resistance and treatment failure.[21] Therefore, medication counselling, compliance follow-up, and pharmacovigilance are essential components of Paxlovid® dispensing.[22]

We did not observe a significant difference in the odds of death between both arms. Two deaths were reported in the Paxlovid® arm, unrelated to COVID-19 infection or Paxlovid® treatment. There were three deaths in the control group, of which two were related to COVID-19 pneumonia. In contrast, Hammond et al. reported a significant difference in all-cause death outcomes, in which no death occurred in the treatment arm and 13 deaths in the placebo arm, of which all were COVID-19 related.[4] Nonetheless, the high number needed to treat in preventing one death suggests the need to investigate the cost-effectiveness of Paxlovid®, particularly in a low-resource health setting.

This study reflected the real-world efficacy of Paxlovid® using a matched cohort, which includes both outpatients and inpatients, vaccinated and unvaccinated populations. Initiation of Paxlovid® was performed using a standard risk-stratified scoring system and closely reflected clinical practice in Malaysian health settings. Several limitations should be considered when interpreting the findings of this study. The small sample size and the exclusion of lost to follow-up cases could restrict the generalisability of the study findings. Furthermore, there was a limited representation of subjects in the over-65 age group. Matching participants based on limited characteristics may introduce bias if other unknown factors influence the outcomes studied.

CONCLUSION

The use of Paxlovid® to treat symptomatic Covid-19 did not significantly reduce the risk of hospitalisation, all-cause death and supplemental oxygen requirement compared to the control group. Adverse events were common but non-severe. The efficacy of Paxlovid® in real-world settings and different populations remains inconsistent and warrants further investigations.

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