

# Paxlovid in Kidney Failure: A Review

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**ABSTRACT:** The COVID-19 virus caused a global pandemic that claimed many lives. Various vaccines and drugs are used for COVID-19 both via intravenous and oral routes. Paxlovid is a treatment given orally to patients who experience symptoms and is even considered effective in reducing high-risk COVID-19 virus infections. Kidney failure is a special population that can worsen COVID-19. The purpose of this review article was to determine the effectiveness and safety of using Paxlovid in patients who have comorbid diseases, one of which is kidney failure. The method used in preparing this journal was the PRISMA diagram to select the right articles and Google Scholar, Pubmed, and ScienceDirect as literature sources. Based on the exclusion and inclusion criteria, around 4 studies were obtained that were appropriate to the research topic. Paxlovid may be an important option to reduce the risk of COVID-19 in at-risk patients and unvaccinated patients, moreover, careful consideration of the benefits and risks to patients can be reviewed.

**Keywords:** COVID-19; dose adjustment; kidney failure; nirmatrelvir/ritonavir; paxlovid



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## 1. Introduction

The first new coronavirus infection occurred in China [1]. By September 24, 2023, more than 770 million infections and total deaths worldwide were expected to exceed approximately 6 million [2]. COVID-19 infection can develop because there are several major risks of diabetes, acute kidney injury (AKI), age, immune deficiency, and cardiovascular disease with a poor prognosis. In addition, this virus has a fairly high level of severity if the patient experiences chronic kidney failure [3].

Around 75% of patients who tested positive for COVID-19, and were hospitalized experienced several abnormalities in their bodies such as acute kidney injury, proteinuria, and even hematuria [4]. The incidence of acute kidney injury patients with novel coronavirus infection ranged from 27 to 45% of cases [5]. In addition, in patients who tested positive for COVID-19, there was a trend of increasing the incidence of AKI and decreasing the risk of eGFR, and the incidence of kidney failure was three times higher than in uninfected patients [5]. Patients with eGFR values of 30 to 60 mL/minute/1.73 m<sup>2</sup> have a 33% risk of death, while patients with eGFR values of less than 30 ml/minute/1.73 m<sup>2</sup> have twice the risk of death compared to patients with normal kidney function [6].

The FDA issued an emergency use authorization in December 2021 to allow treatment of mild to moderate disease in patients infected with COVID-19 with Paxlovid [7]. Paxlovid consists of Nirmatrelvir as a cysteine coronavirus inhibitor such as 3-chymotrypsin and Ritonavir which can inhibit CYP3A and HIV-1 proteases [8]. Paxlovid can shorten the length of hospital stay in COVID-19 patients with AKI [9]. The EPIC-HR study stated that Paxlovid could reduce the death rate or risk of outpatients who were not vaccinated by 89.1% [10].

Studies regarding the effectiveness and safety of Paxlovid in the treatment of COVID-19 in patients with renal impairment are still lacking, so it

is necessary to assess the benefit-risk profile. Antiviral drugs, such as Paxlovid, can provide an effective effect against COVID-19, and considering the important role of Paxlovid in reducing COVID-19 infections, a thorough review of existing evidence and expert opinion is needed to understand the use of paxlovid in renal impairment.

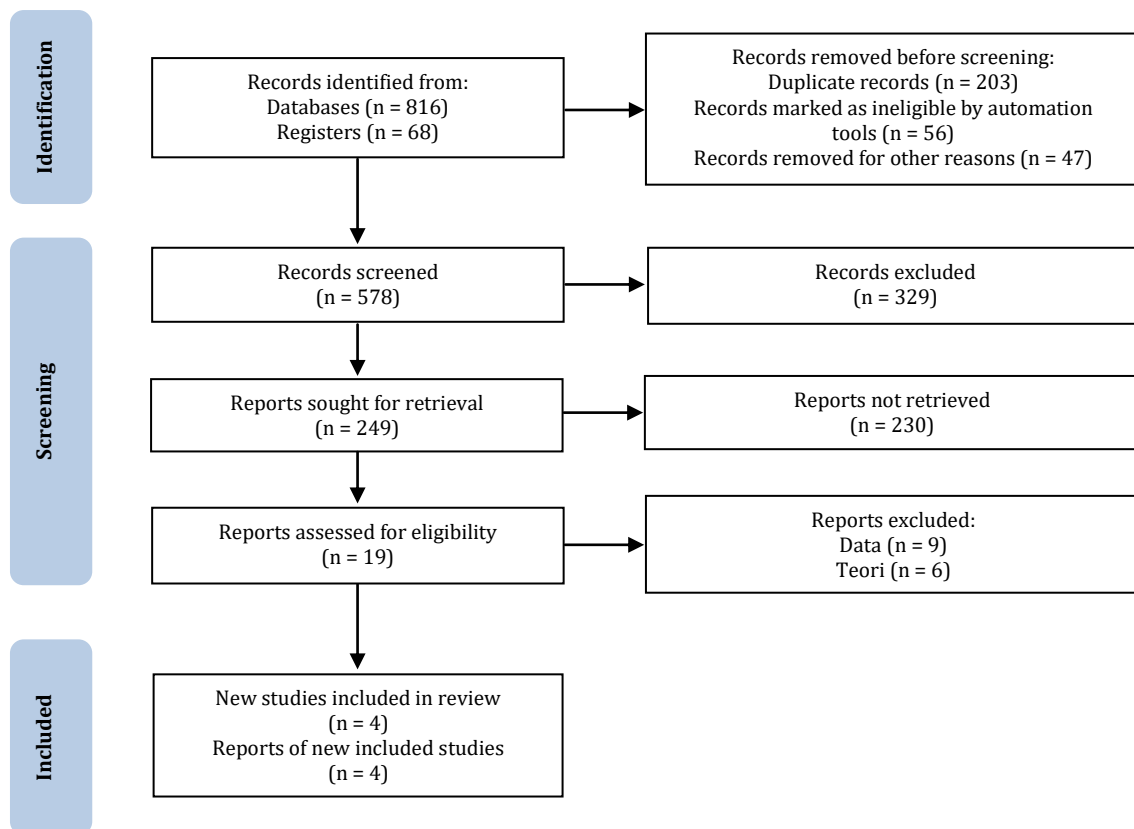
## 2. Materials and methods

In this study, primary literature was used by searching for articles in the database with the keywords Dose Adjustment, COVID-19, Kidney Failure, Paxlovid, Nirmatrelvir, and Ritonavir. The databases were used include Google Scholar, ScienceDirect, Pubmed, and Clinicaltrials.gov. Inclusion criteria and exclusion criteria were used to select journals to be included. The inclusion criteria were: The source of data obtained was an international research journal published in the last 7 years (2016-2023), authors included retrospective descriptive research, ongoing clinical trials in kidney failure patients, cohort studies, original journals, types of research articles in format full text which discussed the use of paxlovid in the kidney failure patients infected with Covid-19. The exclusion criteria in this research were journals that have themes that were not related to the research topic. After that, an analysis of the suitability of the article title with the research objectives was carried out to obtain relevant journals or articles. The PRISMA flow diagram was used to guide the article selection process (Figure 1).

## 3. Results and discussion

### 3.1. Paxlovid In COVID-19

Pharmaceutical companies were racing to develop other antiviral drugs such as Nirmatrelvir [11]. A trial study evaluated protease inhibition of COVID-19 in patients categorized as high risk with a total of 2,246 patients with an 89% reduction in the risk of hospitalization and no deaths,



**Figure 1.** PRISMA flow diagram

while in the placebo group, 7 patients were died [11]. On December 22, 2021, the FDA approved the Nirmatrelvir/Ritonavir combination (Paxlovid) for emergency use [12]. Nirmatrelvir is a reversible covalent inhibitor and Ritonavir is included to maintain effective concentrations of Nirmatrelvir thereby increasing the therapeutic levels [13,14].

The composition of Paxlovid is Nirmatrelvir and Ritonavir [15]. Nirmatrelvir, the antiviral dynamic fixing in Paxlovid, represses the most SARS-CoV-2 protease, Mpro, in this way anticipating the infection from imitating, Ritonavir restrains the digestion system of nirmatrelvir by CYP3A, in this manner expanding the plasma concentration of nirmatrelvir and by itself having no movement against SARS-CoV-2 [16]. Paxlovid had the potential to fight the virus and reduce the death rate by up to 89%. Patients given Paxlovid and vaccination could reduce and prevent the growth of infection thereby reducing the risk of hospitalization [17].

### 3.2. Paxlovid pharmacological profile

#### 3.2.1. Mechanism of action and side effects of Paxlovid

Nirmatrelvir and Ritonavir are two agents combined to form the COVID-19 drug known as Paxlovid [18]. Nirmatrelvir antagonizes the SARS-CoV-2 enzyme 3 – chymotrypsin- like - like cysteine protease (Mpro) [18]. Mpro was identified as a target for antiviral drugs because it plays a role in protein processing and viral pathogenesis, Nirmatrelvir prevents SARS-CoV-2 replication by inhibiting Mpro [19]. Ritonavir is a CYP450 3A4 inhibitor, increasing the bioavailability of Nirmatrelvir within the targeted therapeutic range [20]. The combination of these two drugs aimed to prevent the development of the virus to eliminate viral infections in the early phase of symptoms [21]. Both were also who known effective against the omicron-type variant [22]. In the EPIC-HR interim analysis, Paxlovide was associated with a higher incidence of dysgeusia (4.8% vs 0.1 %), diarrhea (3.9% vs 1.9%), and vomiting (1.3% vs 0.3%) compared to placebo [22]. The FDA does

not recommend Paxlovid in people with severe kidney impairment and impaired liver function because it was known to have the following side effects: nausea, increased blood pressure, diarrhea, vomiting, myalgia, dysgeusia, and headache [23]. Phase 2/3 clinical trials during therapy caused several effects such as hypertension (1%), vomiting (1.3%), diarrhea (3.9)%, and dysgeusia (6%) [23].

### **3.2.2. Paxlovid dosage adjustment in kidney failure**

A study conducted research with Nirmatlevir and Ritonavir in patients undergoing hemodialysis. Interestingly, on the first day of administration of Nirmatlevir/Ritonavir at doses of 300 mg and 100 mg respectively followed by a second dose of 150 mg and 100 mg respectively, these drugs were given daily after undergoing hemodialysis which may show good bioavailability [24]. The eGFR value category  $\geq 60$  to  $< 90$  mL/minute indicated mild renal impairment that did not require dose adjustment. eGFR values in  $\geq 30$  to  $< 60$  mL/minute were included in the moderate category. Paxlovid could be given with a dosage composition of 150 mg Nirmatlevir/100 mg Ritonavir with a regimen of taking it twice a day for 5 days. Renal impairment with an eGFR value  $< 30$  mL/minute was not recommended for administering Paxlovid, because there was no data on the pharmacokinetics and safety of Paxlovid, further research (FDA) was needed [25]. Severe renal impairment caused by Paxlovid triggered an increase in height which could increase the occurrence of the side effects [25].

### **3.3. Paxlovid for hemodialysis patients with COVID-19**

ESRD (*End Stage Renal Disease*) sufferers who undergoing hemodialysis were susceptible to contracting COVID-19 [26]. However, patients undergoing hemodialysis had a higher frequency of incidence and death of COVID-19 than patients did not undergo hemodialysis therapy [27]. In addition, the effectiveness and immunogenicity of the coronavirus vaccine decreased in ESRD patients [28]. WHO strongly recommends Paxlovid

for patients at high risk of hospitalization, as the drug effectively reduced the risk of serious illness [29]. For moderate category patients (eGFR 31 mL-59 mL/minute), it was recommended to be given at a dose of 300 mg/100 mg to 150 mg/100 mg with a frequency of administration twice a day. Patients undergoing hemodialysis with eGFR  $< 30$  mL/minute were not recommended to receive this drug [30]. The criteria for patients that excluded in clinical trials were patients who undergoing dialysis, eGFR  $< 30$ , and organ transplant recipients. This phenomenon called 'renalism', and unfortunately continued with COVID-19 [31]. Based on the available pharmacological data, an adapted therapeutic regimen with Paxlovid with lower doses and longer intervals between doses achieved the required drug concentrations in serum. Available data also did not demonstrate dose-dependent toxicity [32]. Patients diagnosed with ESRD were recently evaluated at doses of Paxlovid 300 mg/100 mg with 150 mg/100 mg, once daily without measurement of pharmacokinetic parameters. However, the dose was well tolerated but there were no pharmacokinetic measurements

### **3.4. Pharmacokinetics of Paxlovid in kidney failure**

Nirmatrelvir is metabolized via CYP3A4, when combined with Ritonavir, there was almost no metabolic damage to Nirmatrelvir, the drug was mostly excreted in the kidneys [33]. Pharmacokinetics of Paxlovid in renal impairment of a phase 1 open-label study in non-randomized patients receiving Paxlovid doses were administered at different hours namely 0, 12, and 24 hours, was performed to compare doses and ensured maximum inhibition of CYP3A4. Eight participants were treated in the patient group with severe, moderate and mild renal impairment, while 10 people were treated in the control group. Nirmatrelvir levels were increased with the severity of renal impairment compared with the mean infusion AUC in the control group in the participants with mild, moderate, and severe renal impairment which was higher by 24%, 87%, and 204%,

respectively. In the renal impairment group, the Cmax values were higher than the control group by 30%, 38%, and 48% for participants with mild, moderate, and, severe renal impairment [34]. Meanwhile, the recommended dose of Nirmatrelvir/Ritonavir for mild renal impairment is 300 mg/100 mg (nCLCR 60 to <90 mL/minute/1.73 m<sup>2</sup>) and 150 mg/100 mg for patients with moderate renal impairment (nCLCR 30 to <60 mL/minute / 1.73 m<sup>2</sup>) while in patients with severe renal impairment, further research is needed [35].

### 3.5. Paxlovid efficacy and safety

A study tested the safety and efficacy of Paxlovid by evaluating the process of protease inhibitors in patients at risk of COVID-19 (EPIC-HR) in non-hospitalized adult patients at mild to high risk of COVID-19 [36]. The group of patients who received Paxlovid on day 28 experienced an 89% lower risk of death or hospitalization compared to the placebo group, 13 deaths were recorded in

the placebo group [36]. Another study also found that Paxlovid was effective and safe for certain populations in a meta-analysis of 13 studies as shown in Table 1 [37]. There were 186,306 infected patients from a total of 13 studies. Five studies in the Paxlovid group and the control group where the overall side effects were 1.07 (95% CI, 0.49–2.34; I<sup>2</sup> = 90%), P = 0.87, so there was no difference in side effects between the two groups. Three other studies observed an increase in COVID-19 patients in the control group vs the Paxlovid group (=59%), P = 0.99 (95% CI, 0.28–3.57; I<sup>2</sup> = 59%). Seven studies looked at patient deaths and hospitalizations in the 2 groups and showed Paxlovid vs control was 0.22 (95% CI, 0.11–0.45; I<sup>2</sup> = 93%), P<0.0001. This result indicated that Paxlovid was effective for COVID-19 patients because it could reduce the risk of hospitalization and death by 78%. The data results showed that Paxlovid was safe and effective to use, there was no significant difference in rebound between the 2 groups [37].

**Table 1.** Effective and safe for certain populations in a meta-analysis

Study	Program	Placebo group		Paxlovid group	
		Event (n)	Number (n)	Event (n)	Number (n)
Yan GF 2022 [38]	Bad incident	7	30	2	5
Anderson USA, 2022 [39]	Bad incident	17	980	23	990
Wang L, 2022 [40]	Bouncing	204	2374	609	11,270
Dai EY, 2022 [41]	Bouncing	1	25	3	11
Li HY, 2022 [42]	Bouncing	3	244	2	258
Wong CKH, 2022 [43]	Death	83	890	31	890
Yep TCF, 2022 [44]	Inpatient	1931	83,154	172	4921
Dryden-PetersonS, 2022 [45]	Death	39	24,286	0	6036
	Inpatient	223	24,286	40	6036
Ganatra S, 2022 [46]	Death	10	1130	0	1130
	Inpatient	23	1130	10	1130
Hedvat J, 2022 [47]	Death	3	75	0	28
	Inpatient	23	75	3	28
Saravolatz LD, 2022 [48]	Death	12	1046	0	1039
	Inpatient	66	1046	8	1039
	Bad incident	22	1046	67	1039
Pfizer; 2021 [49]	Death	12	607	0	612
	Inpatient	66	607	8	612
	Bad incident	22	607	67	612

**Table 2.** Current recommendations regarding the use of Paxlovid in kidney failure

No	Researcher	Method design	Number & type of samples	Results	Death rate
1.	Cai, H <i>et al.</i> , (2023)	A Retrospective Cohort Study	Patient type: mild to moderate Of the 2,387 registrants involved in this study, there were 1,279 people, 658 men and 621 women, with an average age of 60 years. Nirmatrelvir 150 mg and Ritonavir 100 mg, both tablets are taken together twice a day for 5 days. 469 patients (36.7%) of the 1279 participants in this study received Paxlovid and the rest were not treated with Paxlovid	For the mild CKD group, between the group treated with Paxlovid ( $\leq 5$ days and $> 5$ days) and the untreated group there were no significant differences. In contrast, for the severe CKD group, Paxlovid treatment should be started earlier ( $\leq 5$ days) has reduced all mortality causes, invasive ventilation, and ICU admission of patients, respectively, who received Paxlovid; the values were 28 (10.85%) and 26 (10.08%) for the untreated group ( $P = 0.010, 0.035$ , respectively). Secondary outcomes, such as viral elimination within 10 days and ICU admission, occurred in 115 (58.97%) patients still positive and 17 (8.72%) patients in the ICU in the Paxlovid-treated group. The comparable values were 117 (68.60%) and 42 (16.28%) in the untreated group, respectively (OR = 0.66, 95% CI: 0.45-0.97; 0.49, 95 %CI: 0.27-0.89, $P = 0.034, 0.020$ ,)	About twelve (2.6%) patients died in the Paxlovid-treated group, whereas 39 (4.8%) patients died in the untreated group ( $P = 0.066$ ).
2.	Zou <i>et al.</i> , (2023)	Study group	Patient type: moderate-severe A total of 338 OMIC and CKD patients were infected with COVID-19 between 7 December 2022 and 31 January 2023	Use of Paxlovid HR value 95% CI P value respectively 1.46 0.91, 2.35 0.12 The conclusion in this case is the importance of identifying and managing risk factors for COVID-19 comorbidities, especially in the elderly, to optimize clinical outcomes, even after COVID-19 vaccination.	During a average follow-up period of 50 days, 90 patients in the study group died, for a mortality rate of 26.63%. The average age of the study group was 74 years, with a male predominance of 74%.

No	Researcher	Method design	Number & type of samples	Results	Death rate
3.	Chu <i>et al.</i> , (2023)	Retrospective cohort study	Patient type: severe We included 454 and 5,880 patients with CKD stage 4 or greater who received Nirmatrelvir/Ritonavir and Molnupiravir from general clinics and hospitals, respectively.	COVID-19 patients with advanced CKD (eGFR <30 ml/min per 1.37m <sup>2</sup> , including those on dialysis) who received Nirmatrelvir/Ritonavir had a lower mortality rate with all causes at day 90 after treatment compared with those who received molnupiravir	The Nirmatrelvir/Ritonavir group had a significantly lower mortality rate with all causes compared with Molnupiravir group (6.82% vs 10.7%) with an unadjusted HR of 0.67 (95% CI 0.472 - 0.97, p=0.0337*).
4	Lu <i>et al.</i> , 2023	Short research report	Patient Type: mild – severe 20 hemodialysis patients with COVID-19 were screened and 18 were eligible. 14 patients were infected for the first time and 4 patients were infected for the second time.	All patients tolerated 5 days of administration and there were no SAEs or hepatic dysfunction, the C <sub>min</sub> of the drug was higher than that of the control group, and almost half of the patients experienced drug-related side effects, especially gastrointestinal symptoms, and dose-dependent effects. Compared with hemodialysis patients without Nirmatrelvir/Ritonavir, there was no statistical difference in overall viral elimination time (p = 0.232).	No deaths and no serious infections occurred during this period of hospitalization.

### 3.6. Discussion

Renal impairment is one of the factors that can worsen COVID-19 infection and even increase the death rate. Compared with other high-risk groups such as tumors, obesity, people with lung infections, and chronic heart disease, there is a significant increase in the death rate, and kidney function reduction eGFR < 30 ml/minute/1.73 m<sup>2</sup> which has a higher risk of death. Paxlovid specifically improved the prognosis of patients with kidney injury. It helped patients who had comorbidities with kidney disease and were infected with COVID-19, so that Paxlovid can be effective and safe to use.

Paxlovid within 5 days of diagnosis significantly reduced all mortality causes, use of inva-

sive mechanical ventilation, and ICU admission rates compared with patients without the drug consumption. Approximately 85% was reported experiencing one side effect, and 30% was reported get three or more side effects.

Paxlovid could be given with a dosage composition of 150 mg Nirmatlevir/100 mg Ritonavir with a regimen of taking it twice a day for 5 days. Based on the available pharmacological data, an adapted therapeutic regimen with Paxlovid with lower doses and longer intervals between doses might achieved the required drug concentrations in serum. Available data also did not demonstrate dose-dependent toxicity. So the recommended dose of the drug in patients undergoing dialysis was proposed: 300 mg Nirmatrelvir + 100 mg

Ritonavir both on day 1, then 150 mg Nirmatrelvir + 100 mg Ritonavir once daily for the next 4 days, to be given after dialysis. Several trials were also underway to evaluate the use of Paxlovid in COVID-19 patients with kidney failure to study the use of Paxlovid to prevent the progression of severe COVID-19 disease in this vulnerable population.

Paxlovid for COVID-19 was effective and safe, as shown in Table 1. The COVID-19 rebound was not unique to Paxlovid, there was no significant difference between the control group and the Paxlovid group. The rebound phenomenon after Paxlovid treatment highlights the importance of testing for those who experienced recurrent symptoms after treatment. While the recommendations regarding the use of Paxlovid in this condition was mentioned in Table 2.

The trial was conducted using a retrospective method, various confounding factors could cause deviations in the results to address the impact of the patient's disease condition on the prognosis by categorizing the patient's risk of death by factors known to influence the prognosis of COVID-19 (eg CCI), the sample size was limited in terms of statistical analysis subgroup, hospitalization time due to the influence of the patient's family or other reasons. Paxlovid could effectively reduce all mortality causes in patients with kidney injury and reduce the rate of invasive ventilation and ICU admission in patients with severe complications accompanied by kidney injury. Decreased eGFR might prolong viral elimination time and increase mortality in COVID-19 patients, suggesting a rapid reduction in viral load means that Paxlovid may be beneficial for COVID-19 patients with kidney injury. A prospective clinical trial would more accurately determine the benefits and risks of Paxlovid treatment in this patient population. Therefore, it is necessary to carry out further investigation into the research findings by combining data from other regions and research with a larger sample size so that further research is needed.

## 4. Conclusions

Paxlovid that given to patients who have renal impairment has a lower risk of hospitalization or death compared to the group not given Paxlovid. Based on the pharmacological profile of the drug, it is safe and effective to be given to the patients who have mild and moderate renal impairment, while patients who have severe renal impairment are not recommended because further research is still needed regarding the administration of this drug.

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