

Association of Antiviral Drugs for the Treatment of COVID-19 With Acute Renal Failure

MASAHIRO KAMO, RINTARO SOGAWA and CHISATO SHIMANOE

Department of Pharmacy, Saga University Hospital, Saga, Japan

Abstract. *Background/Aim:* Reports regarding the association of remdesivir use for the treatment of Coronavirus disease 2019 (COVID-19) with the development of acute kidney injury (AKI) are inconsistent, and the associations between the use of other antivirals and AKI remain unclear. Therefore, this study investigated whether the use of antiviral drugs for the treatment of COVID-19 is a risk factor for the development of AKI. *Patients and Methods:* This study analyzed 176,197 reports submitted to the Japanese Adverse Event Reporting Database between 2020 and 2022. Reporting odds ratios (RORs) and 95% confidence intervals (95% CIs) for AKI that were associated with the use of antiviral drugs in patients with COVID-19 were calculated after adjusting for potential confounders. *Results:* Overall, 5,879 of the reports analyzed were associated with AKI. Signs of AKI were detected with the use of remdesivir [crude ROR (cROR)=2.45; 95%CI=1.91-3.14] and nirmatrelvir/ritonavir (cROR=6.07; 95%CI=4.06-9.06). These results were maintained even after adjusting for potential confounders [remdesivir: adjusted ROR (aROR)=2.18; 95%CI=1.69-2.80, nirmatrelvir/ritonavir: aROR=5.24; 95%CI=3.48-7.90]. However, when analyzing data stratified by reporting year, the association between remdesivir and AKI appeared to diminish over time and was not sustained. *Conclusion:* Nirmatrelvir/ritonavir use may be associated with developing AKI. This knowledge may be useful in helping patients with COVID-19 avoid AKI complications.

Correspondence to: Rintaro Sogawa, Ph.D., Department of Pharmacy, Saga University Hospital, 5-1-1 Nabeshima, Saga 849-8501, Japan. Fax: +81 952342036, Tel: +81 952316511, e-mail: sogawari@cc.saga-u.ac.jp

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Coronavirus disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has become a global pandemic. However, on May 4, 2023, the World Health Organization announced the end of its declaration of a “public health emergency of international concern”, though mutant strains of COVID-19 continue to emerge and infect individuals. SARS-CoV-2 often causes upper respiratory tract symptoms, including sore throat, nasal discharge, and nasal obstruction, and systemic symptoms, such as fatigue, fever, and myalgia (1). In addition, acute kidney injury (AKI) has been reported as a complication in patients with severe COVID-19 (2). A recent meta-analysis reported that 29% of patients with COVID-19 developed AKI (3). AKI due to COVID-19 is thought to be caused by tubulopenia (4, 5).

In addition, antiviral drugs used as therapy against COVID-19 may also be associated with the development of AKI. Remdesivir, molnupiravir, nirmatrelvir/ritonavir, and ensitrelvir are antiviral drugs that are currently used to treat COVID-19. Remdesivir was the first approved treatment, and renal impairment due to accumulation of the additive sulfobutylether- β -cyclodextrin (SBECD) has been reported (6). In addition, an analysis using the Food and Drug Administration Adverse Event Reporting System (FAERS) has shown an association between remdesivir and AKI (7). In contrast, a meta-analysis reported that remdesivir does not affect the risk of AKI (8). Another previous study revealed that remdesivir can be safely used in patients with an estimated glomerular filtration rate <30 ml/min (9). Remdesivir has been approved by the Food and Drug Administration for the treatment of patients with COVID-19 with severe renal dysfunction, including those requiring dialysis. However, associations between molnupiravir, nirmatrelvir/ritonavir, and ensitrelvir and AKI have not been reported and remain unknown.

The Japanese Adverse Drug Event Report (JADER) database includes data acquired during the post-marketing phase of a drug and is a valuable tool provided by the Japanese regulatory authorities. The JADER database can be used for post-marketing surveillance and reflects the reality of clinical practice. This database is similar to the FAERS



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database in the United States. This study examined the association between AKI and the use of antiviral drugs to treat COVID-19 using reports from the JADER database.

Patients and Methods

Study population. Adverse event reports submitted to the JADER database between January 2020 and December 2022 were downloaded from Japan’s Pharmaceuticals and Medical Devices Agency (PMDA) website. The JADER database, established by PMDA, contains millions of drug adverse event reports that are voluntarily submitted by healthcare professionals and pharmaceutical companies. The original database includes four data tables: patient information, drug information, adverse events, and primary disease. These data tables provide information regarding patient demographics, including sex and age, as well as clinical characteristics such as underlying diseases and concomitant medications. As shown in Figure 1, these tables were combined to extract 206,333 reports. Reports with missing data regarding sex and age (n=30,136) were excluded. The final analysis included 176,197 reports.

Detection of the signal for AKI. In the JADER database, adverse events are coded according to the terminology preferred by the Japanese version of the Medical Dictionary for Regulatory Activities (MedDRA/J) version 26.0. AKI events were identified using preferred terms related to AKI in the Standardized MedDRA Query (SMQ) for acute renal failure (20000003), as described in previous studies (10). Remdesivir, molnupiravir, and nirmatrelvir/ritonavir were selected for inclusion as antiviral drugs against COVID-19 in this study. Ensitrelvir was excluded from this study due to the small number of adverse event reports regarding the use of this antiviral drug. The concomitant uses of non-steroidal anti-inflammatory drugs (NSAIDs; aspirin, acetaminophen, celecoxib, chondroitin sulfate sodium/sodium salicylate, diclofenac, etodolac, flufenamic acid aluminium, flurbiprofen, flurbiprofen axetil, ibuprofen, indomethacin, indomethacin farnesyl, ketoprofen, loxoprofen, meloxicam, mefenamic acid, nabumetone, naproxen, piroxicam, pranoprofen, sodium salicylate, sulindac, and zaltoprofen) (11), calcium channel blockers (CCBs; amlodipine, azelnidipine, barnidipine, benidipine, cilnidipine, diltiazem, efonidipine, felodipine, manidipine, nicardipine, nifedipine, nilvadipine, and nitrendipine), and loop diuretics (LDs; azosemide, furosemide, and torasemide) were also documented. Comorbidities associated with an increased risk of AKI, including hypertension (HT), heart failure (HF), and diabetes mellitus (DM), were also defined by the SMQs in the MedDRA/J. The SMQs of comorbidities included HT (20000147), HF (20000004), and hyperglycemia/new onset DM (20000041). In the JADER database, the contributions of drugs to adverse events are classified into three categories: suspected medication, concomitant medication, and interaction. Antiviral drugs used to treat COVID-19, NSAIDs, CCBs, and LDs were extracted from all categories.

Statistical analyses. All analyses were performed as previously described (10). The reports were divided into four groups: (a) cases identified as AKI with the target medication, (b) cases identified as AKI without the target medication, (c) cases not identified as AKI with the target medication, and (d) cases not identified as AKI

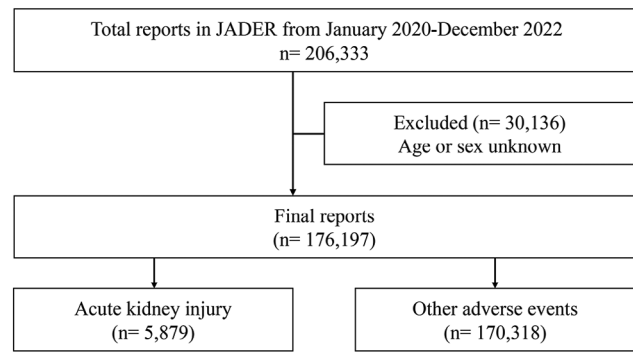


Figure 1. Flowchart depicting the data extraction.

without the target medication. The reporting odds ratios (RORs) and 95% confidence intervals (95% CIs) were calculated using the above groups and the following equations:

$$ROR=(a/b)/(c/d)$$

$$95\%CI=\exp [\log (ROR)\pm 1.96\sqrt{1/a + 1/b + 1/c + 1/d}]$$

For the multivariable logistic regression analysis, the calculated RORs (crude RORs) for antiviral drugs against COVID-19 were adjusted for age (≥ 70 years); sex; reporting year; history of HT, HF, or DM; and medication history including NSAIDs, CCBs, or LDs as the explanatory variable. Moreover, multiple logistic analyses stratified by reporting year were also performed. Statistical significance was defined as a lower limit of the 95% CI of the ROR > 1 . All statistical analyses were performed using JMP17 software (SAS Institute Inc., Cary, NC, USA).

Results

Of the 176,197 reports analyzed in this study, 5,879 described AKI and 170,318 included other adverse events (Figure 1). For all adverse events, 878, 596, and 168 reports listed remdesivir, molnupiravir, and nirmatrelvir/ritonavir, respectively, as suspected drugs. Of these, 68, 20, and 29 included remdesivir, molnupiravir, and nirmatrelvir/ritonavir, respectively, as drugs suspected to be responsible for AKI. Remdesivir (crude ROR=2.45; 95%CI=1.91-3.14) and nirmatrelvir/ritonavir (crude ROR=6.07; 95%CI=4.06-9.06) were associated with AKI, though molnupiravir was not (crude ROR=1.01; 95%CI=0.64-1.57). Patients with existing risk factors, including age (≥ 70 years); sex; history of HT, HF, or DM; and medication history of NSAIDs, CCBs, or LDs had a significantly higher crude ROR for AKI (Table I).

In the adjusted model, remdesivir and nirmatrelvir/ritonavir had a high ROR and were associated with AKI (remdesivir: adjusted ROR=2.18; 95%CI=1.69-2.80; nirmatrelvir/ritonavir: adjusted ROR=5.24; 95%CI=3.48-7.90) (Table II).

Remdesivir was associated with AKI in 2020 (ROR=6.40; 95%CI=4.09-10.0), though the association diminished in

Table I. Comparisons of acute kidney injury (AKI) and other adverse events.

Factors	AKI (n=5,879)	Other adverse events (n=170,318)	Crude ROR (95%CI)
Age (≥ 70 years)	3,294 [56.0]	76,474 [44.9]	1.56 (1.48-1.65)
Sex (male)	3,273 [55.7]	85,853 [50.4]	1.24 (1.17-1.30)
Drugs			
Remdesivir	68 [1.16]	810 [0.48]	2.45 (1.91-3.14)
Molnupiravir	20 [0.34]	576 [0.34]	1.01 (0.64-1.57)
Nirmatrelvir/ritonavir	29 [0.49]	139 [0.08]	6.07 (4.06-9.06)
NSAIDs	806 [13.7]	12,975 [7.62]	1.93 (1.78-2.08)
Calcium channel blockers	801 [13.6]	12,009 [7.05]	2.08 (1.93-2.25)
Loop diuretics	585 [9.95]	6,076 [3.57]	2.99 (2.73-3.27)
History of diseases			
Hypertension	1,123 [19.1]	17,566 [10.3]	2.05 (1.92-2.20)
Heart failure	481 [8.18]	4,272 [2.51]	3.46 (3.14-3.82)
Diabetes mellitus	698 [11.9]	12,298 [7.22]	1.73 (1.60-1.88)

Data are shown as number [percentage]. NSAIDs: Non-steroidal anti-inflammatory drugs; CI: confidence interval; ROR: reporting odds ratio.

Table II. Adjusted reporting odds ratio, (RORs) of antiviral drugs used to treat COVID-19 for acute kidney injury.

Drugs	Adjusted ROR (95%CI)		
	Model 1	Model 2	Model 3
Remdesivir	2.32 (1.81-2.98)	2.17 (1.69-2.80)	2.18 (1.69-2.80)
Molnupiravir	0.94 (0.60-1.46)	0.85 (0.54-1.33)	0.86 (0.55-1.35)
Nirmatrelvir/ ritonavir	5.99 (4.00-8.97)	5.72 (3.80-8.61)	5.24 (3.48-7.90)

CI: Confidence interval. Model 1: Adjusted for age (≥ 70 years), sex, and reporting year. Model 2: Adjusted for the variables in Model 1 and history of hypertension, heart failure, or diabetes mellitus. Model 3: Adjusted for the variables in Model 2 and medication history for use of non-steroidal anti-inflammatory drugs, calcium channel blockers, or loop diuretics.

subsequent years and was not sustained (Table III). In contrast, a consistent robust association between nirmatrelvir/ritonavir and AKI was observed for all years included in this study.

Discussion

The association between antiviral drugs used to treat COVID-19 and AKI development was investigated in this large study, and potential confounders were adjusted for using the JADER database. Remdesivir and nirmatrelvir/ritonavir were found to be associated with AKI, though the association of remdesivir diminished as the study period progressed. FAERS, a similar adverse event spontaneous reporting system, reported that adverse event reports increased over the first two years after approval, but then declined rapidly (12). This may be because

Table III. Reporting odds ratios (RORs) of antiviral drugs used to treat COVID-19 stratified based on the reporting year.

Drugs	Reporting year	Crude ROR (95%CI)	Adjusted ROR (95%CI)
Remdesivir	2020	7.57 (4.88-11.7)	6.40 (4.09-10.0)
	2021	1.96 (1.23-3.12)	1.64 (1.02-2.64)
	2022	1.61 (1.06-2.46)	1.52 (0.99-2.32)
Molnupiravir	2020	–	–
	2021	0.73 (0.27-1.97)	0.63 (0.23-1.70)
	2022	1.15 (0.70-1.90)	0.92 (0.56-1.54)
Nirmatrelvir/ ritonavir	2020	–	–
	2021	3.41 (0.43-27.0)	3.32 (0.41-26.7)
	2022	6.38 (4.23-9.63)	5.51 (3.62-8.39)

CI: Confidence interval. Adjusted for age (≥ 70 years); sex; history of hypertension, heart failure, or diabetes mellitus; and medication history for use of non-steroidal anti-inflammatory drugs, calcium channel blockers, or loop diuretics.

adverse events noted immediately after the time of approval may be more emphasized. From this perspective, the association of nirmatrelvir/ritonavir with the development of AKI in patients with COVID-19 may be more concerning and supports previous reports that remdesivir has no effect on the risk of AKI (8). However, remdesivir contains SBECD, which can cause kidney damage. SBECD is excreted mainly in the urine, and the accumulation of SBECD has been suggested to occur in patients with renal dysfunction (13). The cumulative dose of intravenous voriconazole, which also contains SBECD, is positively associated with decreased renal function (14). However, the time to reach the cumulative dose of voriconazole associated with clinical renal function decline is

assumed to be relatively long. Therefore, even if remdesivir contains SBECD, it may have little effect on renal function for the limited duration of dosing used for the treatment of COVID-19.

In this study, an association between nirmatrelvir/ritonavir and AKI was observed, even after adjustment for potential confounders. A previous study reported that 7% of patients treated with nirmatrelvir/ritonavir developed renal dysfunction (15). The underlying mechanism for this is not clear, though it is possible that ritonavir (including nirmatrelvir/ritonavir) is associated with AKI as an association between ritonavir alone and AKI was observed in the current study (ritonavir: adjusted ROR=6.24; 95%CI=3.03-12.8). Several cases of renal failure have been reported after ritonavir administration (16, 17). In addition, tenofovir, which is used to treat human immunodeficiency virus infections, increases the risk of renal function decline when combined with ritonavir (18). The mechanism for this association remains unclear, though ritonavir is believed to inhibit MRP2, a drug transporter protein, and that protease inhibitors are associated with chronic kidney disease (19, 20). Therefore, monitoring renal function may be important when nirmatrelvir/ritonavir is used to treat COVID-19.

AKI may also be a complication of COVID-19 as SARS-CoV-2 affects a variety of organs, including the kidneys (21). Although the mechanism is not clear, some studies have reported renal proximal tubular dysfunction in patients with COVID-19 (22, 23). Therefore, COVID-19 itself may be contributing to AKI development more than antiviral drugs used to treat COVID-19. In this study, the association between remdesivir and AKI differs based on the reporting year, which may be influenced by changes in the pathogenesis of COVID-19 or the SARS-CoV-2 strain. However, distinguishing between disease and drug effects in this study is difficult as all patients who were treated with antiviral drugs were infected with SARS-CoV-2. A recent retrospective study reported that the incidence of AKI in patients with COVID-19 is higher in patients administered antiviral drugs to treat COVID-19 and that patients with COVID-19 who are administered antiviral drugs and subsequently develop AKI have a worse prognosis than patients who do not (24). To increase the credibility of the results of the current study, the data must be adjusted for differences in COVID-19 pathogenesis and viral strains, and the associations between antiviral drugs used to treat COVID-19 and AKI must be investigated.

This study has several strengths, including its large sample size and ability to detect an association after adjusting for confounding factors including concomitant medications and comorbidities. However, the study also has several limitations. First, the JADER database is a voluntary reporting system. Several biases exist in this system, including underreporting, overreporting, missing data, exclusion of healthy participants, missing denominators for

incidence estimates, and the presence of confounding factors (25, 26). Furthermore, when using an adverse event databases, the risk of AKI cannot be quantified without information regarding the total number of patients treated for COVID-19. Therefore, further clinical studies are needed to validate the results of this study. Second, the accuracy of the AKI diagnosis is limited as a review of medical records in the JADER database could not validate the diagnosis. Third, unadjusted residual confounding factors may have played a role as COVID-19 is associated with countless complications and medications. Indeed, autosomal dominant multiple cystic kidney disease patients infected with COVID-19 have been reported to avoid developing AKI by discontinuing tolvaptan, normalizing urine output, and carefully monitoring weight and fluid administration (27). However, the findings of the current study can be used to support future clinical research.

Conclusion

The results of the current study suggest that nirmatrelvir/ritonavir use may be associated with AKI development in patients with COVID-19 and these findings may be useful in helping patients with COVID-19 avoid AKI complications. However, the results require validation in future studies.

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Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

M.K. and R.S. designed the study and analyzed the data. M.K., R.S. and C.S. drafted the manuscript. All Authors have read and approved the final manuscript.

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References

- Li LQ, Huang T, Wang YQ, Wang ZP, Liang Y, Huang TB, Zhang HY, Sun W, Wang Y: COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. *J Med Virol* 92(6): 577-583, 2020. DOI: 10.1002/jmv.25757

- 2 Chan L, Chaudhary K, Saha A, Chauhan K, Vaid A, Zhao S, Paranjpe I, Somani S, Richter F, Miotto R, Lala A, Kia A, Timsina P, Li L, Freeman R, Chen R, Narula J, Just AC, Horowitz C, Fayad Z, Cordon-Cardo C, Schadt E, Levin MA, Reich DL, Fuster V, Murphy B, He JC, Charney AW, Böttinger EP, Glicksberg BS, Coca SG, Nadkarni GN, on behalf of the Mount Sinai COVID Informatics Center (MSCIC): AKI in hospitalized patients with COVID-19. *J Am Soc Nephrol* 32(1): 151-160, 2021. DOI: 10.1681/ASN.2020050615
- 3 Zhang J, Pang Q, Zhou T, Meng J, Dong X, Wang Z, Zhang A: Risk factors for acute kidney injury in COVID-19 patients: an updated systematic review and meta-analysis. *Ren Fail* 45(1): 2170809, 2023. DOI: 10.1080/0886022X.2023.2170809
- 4 Su H, Yang M, Wan C, Yi LX, Tang F, Zhu HY, Yi F, Yang HC, Fogo AB, Nie X, Zhang C: Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. *Kidney Int* 98(1): 219-227, 2020. DOI: 10.1016/j.kint.2020.04.003
- 5 Ferlicot S, Jamme M, Gaillard F, Oniszczuk J, Couturier A, May O, Grünenwald A, Sannier A, Moktefi A, Le Monnier O, Petit-Hoang C, Maroun N, Brodin-Sartorius A, Michon A, Doboszewicz H, Andreelli F, Guillet M, Izzedine H, Richard C, Dekeyser M, Arrestier R, Sthelé T, Lefèvre E, Mathian A, Legendre C, Mussini C, Verpont MC, Pallet N, Amoura Z, Essig M, Snanoudj R, Brocheriou-Spelle I, François H, Belenfant X, Geri G, Daugas E, Audard V, Buob D, Massy ZA, Zaidan M, AP-HP/Universities/Inserm COVID-19 research collaboration: The spectrum of kidney biopsies in hospitalized patients with COVID-19, acute kidney injury, and/or proteinuria. *Nephrol Dial Transplant: gfab042*, 2021. DOI: 10.1093/ndt/gfab042
- 6 Adamsick ML, Gandhi RG, Bidell MR, Elshaboury RH, Bhattacharyya RP, Kim AY, Nigwekar S, Rhee EP, Sise ME: Remdesivir in patients with acute or chronic kidney disease and COVID-19. *J Am Soc Nephrol* 31(7): 1384-1386, 2020. DOI: 10.1681/ASN.2020050589
- 7 Wu B, Luo M, Wu F, He Z, Li Y, Xu T: Acute kidney injury associated with remdesivir: a comprehensive pharmacovigilance analysis of COVID-19 reports in FAERS. *Front Pharmacol* 13: 692828, 2022. DOI: 10.3389/fphar.2022.692828
- 8 Shams G, Kazemi A, Jafaryan K, Morowvat MH, Peymani P, Karimzadeh I: Acute kidney injury in COVID-19 patients receiving remdesivir: A systematic review and meta-analysis of randomized clinical trials. *Clinics (Sao Paulo)* 78: 100200, 2023. DOI: 10.1016/j.clinsp.2023.100200
- 9 Umemura T, Mutoh Y, Mizuno T, Hagihara M, Kato H, Yamada T, Ikeda Y, Mikamo H, Ichihara T: Safety evaluation of remdesivir for COVID-19 patients with eGFR <30 mL/min without renal replacement therapy in a Japanese single-center study. *Healthcare (Basel)* 10(11): 2299, 2022. DOI: 10.3390/healthcare10112299
- 10 Takeuchi K, Sogawa R, Tsuruhashi S, Motooka C, Kimura S, Shimano C: Antihypertensive drug combinations modify cisplatin-induced acute kidney injury. *In Vivo* 36(3): 1391-1396, 2022. DOI: 10.21873/invivo.12843
- 11 Sharma V, Singh TG: Drug induced nephrotoxicity- A mechanistic approach. *Mol Biol Rep* 50(8): 6975-6986, 2023. DOI: 10.1007/s11033-023-08573-4
- 12 Hoffman KB, Dimbil M, Erdman CB, Tatonetti NP, Overstreet BM: The Weber effect and the United States Food and Drug Administration's Adverse Event Reporting System (FAERS): analysis of sixty-two drugs approved from 2006 to 2010. *Drug Saf* 37(4): 283-294, 2014. DOI: 10.1007/s40264-014-0150-2
- 13 Luke DR, Tomaszewski K, Damle B, Schlamm HT: Review of the basic and clinical pharmacology of sulfobutylether- β -cyclodextrin (SBECD). *J Pharm Sci* 99(8): 3291-3301, 2010. DOI: 10.1002/jps.22109
- 14 Yasu T, Konuma T, Kuroda S, Takahashi S, Tojo A: Effect of cumulative intravenous voriconazole dose on renal function in hematological patients. *Antimicrob Agents Chemother* 62(9): e00507-18, 2018. DOI: 10.1128/AAC.00507-18
- 15 González-Gómez Á, Caro-Teller JM, González-Barrios I, Castro-Frontiñán A, Rodríguez-Quesada PP, Ferrari-Piquero JM: Safety profile of nirmatrelvir-ritonavir: Evidence of adverse events due to drug-drug interactions. *Farm Hosp*, 2023. DOI: 10.1016/j.farma.2023.08.005
- 16 Chugh S, Bird R, Alexander EA: Ritonavir and renal failure. *N Engl J Med* 336: 138, 1997. DOI: 10.1056/NEJM19971093360214
- 17 Deray DG: Ritonavir-induced acute renal failure. *Clin Drug Investig* 16(2): 175, 1998. DOI: 10.2165/00044011-199816020-00012
- 18 Goicoechea M, Liu S, Best B, Sun S, Jain S, Kemper C, Witt M, Diamond C, Haubrich R, Louie S, California Collaborative Treatment Group 578 Team: Greater tenofovir-associated renal function decline with protease inhibitor-based *versus* nonnucleoside reverse-transcriptase inhibitor-based therapy. *J Infect Dis* 197(1): 102-108, 2008. DOI: 10.1086/524061
- 19 Cihlar T, Ray AS, Laflamme G, Vela JE, Tong L, Fuller MD, Roy A, Rhodes GR: Molecular assessment of the potential for renal drug interactions between tenofovir and HIV protease inhibitors. *Antivir Ther* 12: 267-272, 2007.
- 20 Mocroft A, Kirk O, Reiss P, De Wit S, Sedlacek D, Beniowski M, Gatell J, Phillips AN, Ledergerber B, Lundgren JD, EuroSIDA Study Group: Estimated glomerular filtration rate, chronic kidney disease and antiretroviral drug use in HIV-positive patients. *AIDS* 24(11): 1667-1678, 2010. DOI: 10.1097/QAD.0b013e328339fe53
- 21 Legrand M, Bell S, Forni L, Joannidis M, Koyner JL, Liu K, Cantaluppi V: Pathophysiology of COVID-19-associated acute kidney injury. *Nat Rev Nephrol* 17(11): 751-764, 2021. DOI: 10.1038/s41581-021-00452-0
- 22 Aroca-Martínez G, Avendaño-Echavez L, Garcia C, Ripoll D, Dianda D, Cadena-Bonfanti A, Musso CG: Renal tubular dysfunction in COVID-19 patients. *Ir J Med Sci* 192(2): 923-927, 2023. DOI: 10.1007/s11845-022-02993-0
- 23 Werion A, Belkhir L, Perrot M, Schmit G, Aydin S, Chen Z, Penalzoza A, De Greef J, Yildiz H, Pothen L, Yombi JC, Dewulf J, Scohy A, Gérard L, Wittebole X, Laterre PF, Miller SE, Devuyt O, Jadoul M, Morelle J, Cliniques universitaires Saint-Luc (CUSL) COVID-19 Research Group: SARS-CoV-2 causes a specific dysfunction of the kidney proximal tubule. *Kidney Int* 98(5): 1296-1307, 2020. DOI: 10.1016/j.kint.2020.07.019
- 24 Mousavi Movahed SM, Akhavizadegan H, Dolatkhani F, Akbarpour S, Nejadghaderi SA, Najafi M, Pezeshki PS, Khalili Noushabadi A, Ghasemi H: Incidence of acute kidney injury (AKI) and outcomes in COVID-19 patients with and without antiviral medications: A retrospective study. *PLoS One* 18(10): e0292746, 2023. DOI: 10.1371/journal.pone.0292746

- 25 Ishibashi Y, Sogawa R, Ogata K, Matsuoka A, Yamada H, Murakawa-Hirachi T, Mizoguchi Y, Monji A, Shimanoe C: Association between antidiabetic drugs and delirium: a study based on the adverse drug event reporting database in Japan. *Clin Drug Investig* 44(2): 115-120, 2024. DOI: 10.1007/s40261-023-01337-9
- 26 Van Puijtenbroek EP, Bate A, Leufkens HGM, Lindquist M, Orre R, Egberts ACG: A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions. *Pharmacoepidemiol Drug Saf* 11(1): 3-10, 2002. DOI: 10.1002/pds.668
- 27 Capelli I, Iacovella F, Ghedini L, Aiello V, Napoletano A, Marconi L, Viale P, Masina M, LA Manna G: A case report of tolvaptan therapy for ADPKD patients with COVID-19. The need for appropriate counselling for temporary drug discontinuation. *In Vivo* 36(4): 1994-1997, 2022. DOI: 10.21873/invivo.12924

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