Review

Pharmacotherapy Considerations in CKD Patients With COVID-19, A Narrative Review

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Treatment of coronavirus disease 2019 (COVID-19) among patients with CKD requires special pharmacotherapy considerations that are reviewed here.

Literature review was done for several pharmacotherapy aspects in CKD patients including selection and modification of COVID-19 treatment, drug interactions, nephrotoxicity of drugs that are used for treatment of COVID-19 and potential risks/benefits of routine medications of CKD patients during COVID-19 pandemic.

CKD patients should be treated according to local or national COVID-19 protocols as other patients. But, there is no data on using remdesivir in patients with severe CKD. Oseltamivir and ribavirin require dose modification in patients with moderate to severe CKD. Nephrolithiasis, CKD, and acute interstitial nephritis have been reported with protease inhibitors. Acute kidney injury has been reported with remdesivir in patients with severe COVID-19. Pharmacokinetic-enhanced protease inhibitors increase the concentration of some drugs such as statins, cinacalcet, steroids, calcineurin inhibitors (CNIs). Some hypothetical benefits and harms have been suggested for statins and renin-angiotensin-aldosterone system inhibitors in COVID-19 patients. Continuing guideline-directed administration of these drugs is recommended. Among different immunomodulating/immunosuppressive drugs, hydroxychloroquine and CNIs are the safest ones during COVID-19. Antimetabolites are suggested to be withheld during moderate to severe COVID-19. Fluid therapy and anticoagulant prophylaxis/treatment need special attention in CKD patients with COVID-19. CKD patients with COVID-19 are treated as other patients, with some dose modifications if needed. Be mindful for management of drug interactions as well as modification of immunosuppressive drugs in patients with moderate to severe COVID-19.

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INTRODUCTION

New coronavirus pandemic named coronavirus disease 2019 (COVID-19) causes by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] Patients with diabetes mellitus, hypertension, and cardiovascular diseases have been introduced as high risk patients for COVID-19.[2] Diabetes and hypertension are common causes of chronic kidney disease (CKD).[3] Hence, it is expected that patients with CKD be at increased risk for COVID-19. Treatment of COVID-19 among CKD patients requires special pharmacotherapy considerations that have been reviewed here in several aspects including modification of COVID-19 treatment

regimen for patients with impaired kidney function, management of drug interactions in these patients due to common polypharmacy among patients with CKD, attention to nephrotoxicity of COVID-19 treatment regimen and possible need for modification of commonly used drugs among CKD patients. Pharmacotherapy considerations in kidney transplant patients are not discussed here.

RISK FOR COVID-19 AMONG CKD PATIENTS

There is no exact data on the incidence of CKD as comorbidity among patients with COVID-19. A survey on 1099 patients with laboratory-confirmed COVID-19 from 552 hospitals in 30 provinces, China revealed that only 0.7% of the patients had pre-existing CKD disease.[2] Despite this low reported rate of CKD among patients with COVID-19, a meta-analysis on 4 studies consisting 1389 patients showed significant association between CKD and severe COVID-19 (OR = 3.03, 95% CI: 1.09 to 8.47).[4] Angiotensin converting enzyme (ACE) 2 that is the functional receptor for SARS-CoV-2 and its cellular invasion is expressed in podocytes and proximal convoluted tubules, therefore, kidney is expected to be an important organ for SARS-CoV-2 induced cytopathic and inflammatory damage.[5,6] But, the rate of acute kidney injury (AKI) is not so high in hospitalized patients with COVID-19. In a report on 1099 patients from China, AKI happened in 0.5% of hospitalized patients.[2] A systematic review and meta-analysis on 19 studies consisting 660 patients with COVID-9 showed that 7.9% of patients experienced AKI.[7] Another retrospective, observational, multicenter study on 193 patients with laboratory-proven COVID-19 in China showed that at hospital admission 59% of the patients had proteinuria, 44% had hematuria, 14% had increased blood urea nitrogen (BUN), and 10% showed elevated serum creatinine concentration. Since previous medical histories of the patients were not exactly available, all of these findings cannot be readily diagnosed as AKI due to COVID-19; however, a multivariate analysis revealed that proteinuria, hematuria, and elevated BUN and creatinine concentrations were significantly correlated with death in patients with COVID-19.[8] AKI has been reported as a lethal complication among patients with COVID-19 in another survey as well.[9]

TREATMENT OF COVID-19 IN CKD PATIENTS

There is no specific pharmacologic treatment for SARS-CoV-2. Several antimicrobial and anti-inflammatory/adjuvant drugs are being used under clinical trial or compassionate use protocols. These drugs have been chosen based on in vitro activity against SARS-CoV-2 or other members of coronavirus family and/or some limited clinical experiences. These drugs include chloroquine/hydroxychloroquine, remdesivir, protease inhibitors (lopinavir/ritonavir, atazanavir, darunavir/cobicistat), favipiravir, arbidol (umifenovir), oseltamivir, azithromycin, sofosbuvir, tocilizumab, interferon (alpha and beta), and intravenous immunoglobulin.[10] Patients with creatinine clearance of less than 50 (NCT04292899) or 30 mL/min (NCT04257656, NCT04280705, NCT04323761) have been excluded from remdesivir clinical trials in patients with COVID-19.[11] Tocilizumab has not been studies in patients with creatinine clearance of less than 30 mL/min.[12] Other drugs are not contraindicated in patients with underlying kidney disease but some of them needs dose modification based on the level of kidney function.[12] Therefore, patients with underlying kidney diseases can be treated according to local or national COVID-19 protocols as other patients; but, more data is needed before using remdesivir and tocilizumab in patients with severe CKD.

DOSE ADJUSTMENT OF COVID-19 TREATMENT REGIMEN IN CKD PATIENTS

Lopinavir/ritonavir, atazanavir, darunavir/cobicistat, arbidol, sofosbuvir, and azithromycin do not require dose adjustment in patients with CKD.[12,13] Fifty percent dose reduction has been suggested for hydroxycholoquine in lupus nephritis patients with creatinine clearance of less than 30 mL/min.[12,14] Half routine dose of chloroquine has been suggested for patients with creatinine clearance of less than 10 mL/min and those on maintenance hemodialysis or peritoneal dialysis.[12] Dose modification of hydroxychloroquine has been proposed for patients who are taking these drugs chronically[12,14] and may not be extrapolated to short-course treatment of COVID-19.

Oseltamivir dose has to be reduced from 75 mg twice daily to 30 mg twice daily in patients

with creatinine clearance of less than 60 mL/min and to 30 mg/d in CKD patients with creatinine clearance of less than 30 mL/min. For patients on intermittent maintenance hemodialysis doses of 75 mg and 30 mg after each dialysis session have been proposed for dialysis with high-flux and low-flux membranes, respectively. For patients on continuous ambulatory peritoneal dialysis it has been postulated that a single 30 mg dose is sufficient for a 5-day treatment course.[12]

Remdesivir had not been previously approved by US food and drug administration (FDA) or European Medical Agency (EMA) for any indication. It is administered intravenously with a dose of 200 mg in the first day and then 100 mg daily for 9 days under clinical trial or compassionate protocols. Patients with creatinine clearance of less than 50 (NCT04292730, NCT04292899) or 30 mL/min (NCT04323761, NCT04252664) have been excluded from remdesivir clinical trials in patients with COVID-19. Therefore, no data would be available for remdesivir in patients with severe CKD.[11,15]

Favipiravir has been approved for treatment of influenza in Japan. It has not been approved by US FDA or EMA for any indication. So, enough data on its dose adjustment in CKD patients is not available. At least three clinical trials have been submitted for using favipiravir in COVID-19. Different doses have been applied *e.g.* 1600 mg twice daily for the first day of treatment, followed by 600 mg twice daily thereafter usually for 1 week (NCT04310228, NCT04333589) or 2400-2400-1200 mg for the first day, 8 hours apart followed by 1200 mg twice daily from the second day of treatment (NCT04303299). These studies have not excluded CKD patients from the study with these favipiravir doses. Only one of them excluded patients with unstable kidney function (NCT04333589) (probably AKI not CKD).[11]

Ribavirin was used in the regimen of COVID-19 at the beginning of SARS-CoV-2 outbreak; however, it is not used in newer COVID-19 regimens. It has been used with doses of 1000 to 1200 mg twice daily or 600 to 800 mg three times a day. Dose reductions of 50% and 75% have been proposed for patients with creatinine clearance between 30 to 50 mL/min and less than 30 mL/min, respectively in patients with SARS.[16] Tocilizumab has been approved for rheumatoid arteritis and cytokine release syndrome. It has not been studied in patients with creatinine clearance of less than 30 mL/min.[12]

NEPHROTOXICITY OF DRUGS THAT ARE USED FOR TREATMENT OF COVID-19

Some drugs that are used in COVID-19 treatment regimen (such as remdesivir, favipiravir, arbidol) have not been approved previously by US FDA or EMA, so; there is no data on their potential nephorotoxicity. Chloroquine/hydroxychloroquine, azithromycin, oseltamivir, and interferons have no considerable nephrotoxicity.[12]

Ritonavir boosted protease inhibitors such as lopinavir/ritonavir and atazanavir/ritonavir have been associated with increased risk of CKD in less than 1% of patients taking these drugs. This side effect has been seen in the median time of 4.5 years (inter-quartile range (IQR) 2.7 to 6.1 years) of follow-up.[17] Atazanavir can cause crystalluria/urolithiasis in a median time of 24.5 months (IQR 14.7 to 34.6 months) after commencement.[18] In addition, acute interstitial nephritis has been reported with atazanavir.[19] However, short duration of administration of these drugs for treatment of COVID-19 decreases the risk of renal side effects of these protease inhibitors.

Sofosbuvir may induce AKI in the form of acute interstitial nephritis with varying incidence of 1 to 15%. The median time of 9 weeks from the beginning of sofosbuvir to AKI occurence has been reported.[20] Therefore, short treatment period of COVID-19 eliminates the concern of sofosbuvir induced acute interstitial nephritis.

AKI has been reported as a major side effect of remdesivir among patients with severe COVID-19. This adverse effect has been mostly seen in patients under invasive mechanical ventilation.[21]

Nephrolithiasis has been reported in less than 2% of the patients taking tocilizumb, however; most of the patients with this side effect were those with rheumatoid arteritis who were taking methotrexate concomitantly. Methotrexate has been well known for inducing nephrolithiasis.[12]

Acute kidney injury has been reported in less than 1% of patients who receive intravenous immunoglobulin. In patients with underlying kidney dysfunction the infusion rate and concentration of the intravenous immunoglobulin solution have to be reduced.[12]

MANAGEMENT OF INTERACTION BETWEEN ROUTINE DRUGS OF THE CKD PATIENTS WITH COVID-19 TREATMENT REGIMEN

Some protease inhibitors (*e.g.* lopinavvir, darunavir) and their pharmacokinetic enhancers (ritonavir and cobicistat) are potent inhibitors of both cytochrome (CYP) 450 3A isoenzymes and P-glycoprotein efflux pump. These two systems play major roles in the metabolism and cellular distribution of several drugs; some of them are widely used by CKD patients.[12,22]

Cinacalcet

Cinacalect is metabolized by CYP450 3A. Cinacalcet concentration and exposure increase in patients taking lopinavir/ritonavir, atazanavir/ritonavir or darunavir/cobicistat. Although, serum level of parathyroid hormone may not change rapidly during only several days coadministration of cinacalcet with these ritonavir/ cobicistat -boosted protease inhibitors, rapid presenting side effects of cinacalcet such as hypocalcemia and hypomagnesemia may develop. These electrolyte abnormalities intensify the QT prolongation adverse effect of lopinavir/ritonavir or atazanivir/ritonavir especially if these antiviral drugs are used in a regimen containing chloroquine/hydroxychloroquine as well.[12,22]

Statin

Many patients with nephrotic syndrome take statins. CKD patients with different types of cardiovascular diseases also receive statins.[3] Most statins are metabolized by CYP450 3A and their exposure increases if coadministered with pharmacokinetic-enhanced protease inhibitors. Coadministration of simvastatin or lovastatin with ritonavir/cobicistat boosted protease inhibitors should be avoided. Due to increased systemic exposure to atorvastatin and rosuvastatin by about 490% and 108%, respectively when coadministered with pharmacokinetic-boosted protease inhibitors; maximum daily doses of 20 mg for atorvastatin and 10 to 20 mg for rosuvastatin have been proposed in patients taking these two drug classes concomitantly. Systemic exposure to pitavastatin and pravastatin increases by about 30% if taken with protease inhibitors. No dose adjustment was recommended for these two statins in combination with pharmacokinetic-enhanced protease inhibitors. It is prudent to monitor patients taking statins in combination with ritonavit/cobicistat-boosted protease inhibitors regarding myopathies, creatine phosphokinase elevation and possibly rhabdomyolysis and AKI. Keep in mind that these signs and symptoms are common between COVID-19 and statin toxicity.[12,22,23]

Corticosteroids

Patients with glomurelunephritis or vasculituies are usually treated with intravenous methylprednisolone pulse and oral prednisone/prednisolone. Pharmacokinetic-boosted protease inhibitors increase steroid exposure and adverse effects.[12,22]

Calcineurin Inhibitors

Pharmacokinetic-boosted protease inhibitors impede metabolism of calcineurin inhibitors (CNIs). A significant decline of 80% to 95% in cyclosporine dose or dose reduction of tacrolimus to about 1mg weekly and close blood concentrations monitoring of CNIs are recommended. Chloroquine/hydroxychloroquine also can increase CNIs blood concentration by inhibiting CNIs metabolism. In contrast, tocilizumab decreases CNIs concentrations by inducing CYP450 3A.[12,22]

Azathioprine

Hematologic toxicities of azathioprine may be enhanced in combination with chloroquine/hydroxychloroquine. Ribavirin can interfere with azathioprine metabolism and increase myelotoxic metabolites of azathioprine. Ribavirin has its own hematologic toxicity as well that exacerbate cytopenia in patients treating with these two drugs concomitantly. Enhanced myelotoxicity may also happen in coadministration of azathioprine with tocilizumab or interferons.[12,22] Patients should be monitored for blood cells counts.

Mycophenolate Mofetil/Sodium

Mycophenolate[12] and COVID-19[2] have hematologic side effects in common. Although chloroquine/hydroxychloroquine has hematologic side effects[12] and despite long term use of mycophenolate and hydroxychloroquine in patients with lupus nephritis,[13] no interaction has been reported between these two drugs in the literature.[12,22]

HYPOTHETICAL BENEFITS/HARMS OF SOME ROUTINE DRUGS OF CKD PATIENTS ON SEVERITY OF COVID-19

Renin-angiotensin-aldosterone system inhibitors

SARS-CoV-2 uses ACE2 as a functional receptor for cell entry. ACE2-bound SARS-CoV-2 internalization causes ACE2 down-regulation and subsequent overexpression of angiotensin II (AngII) and AT1 receptor in the lung and heart and damages to these tissues. Based on above findings, some researchers hypothesized that ACE inhibitors or angiotensin receptor blockers (ARBs) could be possible options to reduce SARS-CoV-2 induced lung injury.[24] This hypothesis has not been assessed in experimental or clinical studies. While ACE2 down-regulation by the virus may promote AngII and AT1 receptor expression, using ACE inhibitors and ARBs also increase AngII expression by several times. In addition, ACE2 is not inhibited by ACE inhibitors.[25] Therefore, using renin-angiotensin system inhibitors to prevent or treat COVID-19 may provide more ACE2 available for SARS-CoV-2 spike protein to bind and invade the lung and cardiac cells. Some investigators concern regarding harmful effects of these drugs in COVID-19 patients because of increased ACE2 levels in the lungs and heart by these drugs.[26] There is no scientific evidence to support this suggestion as well. Taken together, at this time it is recommended not initiating ACE inhibitors or ARBs to prevent or treat COVID-19. Several specialty societies recommend continuing these drugs during COVID-19 outbreak in patients who were taking them due to definite cardio- and nephroprotective indications such as history of myocardial infarction, heart failure, hypertension or proteinuria.[27] Another aspect that should be taken into account is AKI as a severe complication among patients with COVID-19. It may be at least partly due to high expression of ACE2 in podocytes and proximal convoluted tubules that make kidney as an important organ for SARS-CoV-2 induced cytopathic and inflammatory damage.[5] ACE inhibitors and ARBs may also cause AKI especially during initiation and dose escalation. Dose adjustment or even temporary discontinuation of ACE inhibitors/ARBs may be required in patients with severe AKI and subsequent hyperkalemia.[28]

Statins

Some human and animal studies revealed lung injury improvement by statins due to anti-inflammatory effects of these drugs.[29,30] In contrast, a retrospective study on the efficacy of rosuvastatin against infection-induced ARDS showed higher mortality in statin treated patients possibly because of increased IL-18.[31] During current COVID-19 pandemic some US hospitals included statin in their treatment regimen[32] and some suggested their use.[33,34] On the other hand, some others worry about statin-induced increase IL-18 level and worsening of SARS-CoV-2 induced ARDS and mortality.[35]

Large number of CKD patients suffers diabetes or cardiovascular diseases and should receive statin. Therefore, guideline-directed continuations of statin therapy among COVID-19 patients with history of atherosclerotic cardiovascular disease or diabetes and guidance-directed initiation of statin in patients with COVID-19 who show acute cardiac injury have been recommended. But, staring statin for management of COVID-19 infection outside clinical trial protocols is not suggested.[23]

FLUID THERAPY IN CKD PATIENTS WITH COVID-19

In the absence of shock, conservative fluid management is recommended in COVID-19 patients with severe acute respiratory infection or acute respiratory distress syndrome (ARDS). Excessive fluid administration may worsen oxygenation in these patients. For patients in septic shock, bolus dose of 250 to 500 mL crystalloid solutions over 15 to 30 minutes is recommended. Additional fluid should be administered after assessment for signs of overload.[36]

MODIFICATION OF IMMUNOSUPPRESSIVE/IMMUNOMODULATORY DRUGS IN CKD PATIENTS WITH COVID-19

Hydroxychloroquine

Almost all patients with lupus nephritis are treated with hydroxychloroquine.[14] Hydroxychloroquine has been used in COVID-19 treatment regimens as well.[10] So, CKD patients who are treated with hydroxychloroquine should continue this drug during COVID-19 pandemic and infection episode.

Corticosteroids

Large number of CKD patients with glomerulonephritis or vasculitis takes maintenance oral prednisolone/prednisone and during disease flare receives intravenous steroid pulse.[3,14] Steroids may prolong viral shedding, therefore, are not recommended for the treatment of patients with mild to moderate COVID-19 unless other indication such as exacerbation of asthma or obstructive pulmonary disease is present. Steroids are used for treating severe COVID-19 patients with septic shock or ARDS.[36] Some experts propose administering least effective maintenance dose of prednisolone/prednisone during COVID-19 pandemic in CKD patients who were already treating with these drugs. Increased steroid dose or changing oral steroid to intravenous one during severe COVID-19 infection and ARDS is recommended in kidney disease patients on chronic steroid therapy.[37]

CNIs

Some *in vitro* antiviral activities have been reported for cyclosporine against some members of coronavirus family.[10,38] Considering risks of the flare of underlying kidney disease, it seems prudent to continue CNIs especially cyclosporine with the lowest effective dose.[37] Balancing the risk of flare of the underlying kidney disease and severity of COVID-19 infection, one may consider switching from other immunosuppressive drugs to cyclosporine if there is efficacy for cyclosporine in that situation. However, AKI is a complication that may be seen with both COVID-19[2] and CNIs.[39]

Mycophenolate / Azathiopurine

The results regarding antiviral effects of mycophenolate are conflicting.[38,40] Fatal outcome has been reported with this drug during previous viral outbreaks.[38] On the other hand, mycophenolate has adverse hematologic effects including leukopenia and thrombocytopenia that may exacerbate hematologic complications of COVID-19.[2,38] Since available data shows no higher incidence of COVID-19 among CKD patients compared with other populations, it seems logical to continue mycophenolate in CKD patients taking this drug for glomerulonephritis or vasculitis diseases. In patients with severe COVID-19, it is suggested to stop antimetabolites including mycophenolate and azathioprine.[37]

Cyclophosphamide / Rituximab

ERA/EDTA recommends postponing the administration of maintenance cyctotoxic drugs/rituximab in patients with glomerulonephritis or vasculitis, however, disease flare may be detrimental.[37]

ANTICOAGULATION IN CKD PATIENTS WITH COVID-19

Patients with severe COVID-19 are at increased risk for thrombosis because of inflammation, immobility, hypoxia-induced thrombosis, and possibly invasion of the virus into the endothelial cells.[41] In a retrospective study on 449 patients with severe COVID-19, 28-day mortality was compared between patients who received and not received prophylactic doses of unfractionated (UFH) or low molecular weight heparin (LMWH). In general, mortality did not differ between these two groups of the patients. But, in patients with sepsis induced coagulopathy score[42] of more than 4 or D-dimer of more than 6 times of upper normal limit, 28-day mortality was significantly lower in heparin product users.[43] In addition to anticoagulation effects, heparin derivatives possess anti-inflammatory effect[44] that may be of benefit in COVID-19 patients who fulfill criteria for receiving prophylactic or treatment doses of heparins. World health organization recommends thromboembolism prophylaxis using LMWH (preferred) or UFH for critically ill patients with COVID-19 with no contraindication for heparin administration.[36] Based on available data, International Society of Thrombosis and Haemostasis (ISTH) has recommended the prophylactic dose of LMWH for every patient with COVID-19 who requires hospitalization. ISHT considered only active bleeding and platelet count of less than 25×10^9 /L as contraindications for LMWH administration.[45] CKD is a double-edged sword situation for thrombosis and hemorrhagic events.[46] Due to renal elimination of LMWH, unfractionated heparin is usually preferred in CKD patients with creatinine clearance of less than 30 mL/min or those who experience AKI during infection episode. However, dose reduction to 1 mg/kg/d for treatment and 20 to 30 mg/d for thrombosis prophylaxis has also been proposed for enoxaparin in CKD patients with creatinine clearance of less than 30 mL/min.[12,46] ISTH did not exclude patients with severe

CKD from its recommendation for thrombosis prophylaxis using LMWH and only recommended patient and laboratory monitoring.[45]

CONCLUSION

CKD patients should be treated according to local or national COVID-19 protocols as other patients. Due to lack of data in patients with severe CKD, remdesivir and tocilizumab are not suggested in patients with severe CKD. Oseltamivir and ribavirin require dose modification in patients with moderate to severe CKD.

Nephrolithiasis, CKD and acute interstitial nephritis have been infrequently reported with some protease inhibitors; however, due to the short period of COVID-19 treatment, there is no concern for these renal side effects. Pharmacokinetic-boosted protease inhibitors increase the concentration of some drugs such as statins, cinacalcet, steroids, and CNIs that are frequently used in patients with kidney diseases. The dose of these drugs should be reduced and their side effects be monitored. Some hypothetical benefits and harms have been proposed for statins and inhibitors of renin-angiotensin-aldosterone system in patients with COVID-19. Specialty societies recommend continuing these drugs in CKD patients who were already taking them during COVID-19 infection. They also recommend guideline-directed starting of these drugs in patients with COVID-19; however their side effects that are in common with clinical/laboratory characteristics of COVID-19 (such as AKI or myopathy) should be kept in mind. CKD patients who are taking hydroxychloroquine should continue this drug during COVID-19 pandemic and infection. Among different immunosuppressive drugs, CNIs are the safest ones during COVID-19 pandemic and infection. Antimetabolites are recommended to be withheld during moderate to severe COVID-19 infection. Some specialty societies recommend postponing administration of cytotoxic drugs and rituximab. But, clinicians should be mindful for the risk of underlying disease flare. Fluid therapy in hospitalized CKD patients with COVID-19 should be done conservatively. Fluid resuscitation in patients with shock should be done with small bolus of crystalloid solutions. Excessive fluid administration deteriorates oxygenation and increases the risk of ARDS. Prophylactic anticoagulation with heparin derivatives is recommended in CKD patients with COVID-19 who are admitted in the hospital. Report and studies on the efficacy and safety of drugs that are used in COVID-19 treatment regimen in CKD patients are emergently needed. Appropriate modification of immunosuppressive drugs requires sharing experiences of different hospitals worldwide.

CONFLICT OF INTEREST

Authors declare no competing interest.

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AUTHORS CONTRIBUTIONS

SDK contributed in conceptualization, literature review, data gathering and interpretation, manuscript writing, drafting, and finalization.

HK contributed in literature review, data gathering and interpretation, supervision, manuscript writing, drafting and finalization.

AN contributed in literature review and manuscript drafting.

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