

The Impact of CKD on the Prognosis of COVID-19: A Protocol for Systematic Review and Meta-analysis

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Protocol

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Abstract

Background: COVID-19 is a serious respiratory disease currently causing a global pandemic. However, few studies have evaluated the prognosis of chronic kidney disease (CKD) patients infected with COVID-19. Given the comorbidities evident in CKD patients, we speculate that they are more likely to be susceptible to COVID-19 infection relative to healthy individuals. However, a systematic study is necessary to confirm the relationship between these two conditions.

Methods: The Wanfang, China Science Journal Citation Report (VIP database), EMBASE, CNKI, Web of Science, PubMed, and Cochrane Library databases will be reviewed to identify relevant studies. The PRISMA-P and Cochrane Handbook guidelines were used to prepare a standardized table to extract data from all relevant studies in a uniform manner. Risk and quality assessment analyses will be conducted for all included studies, with Revman 5.3 and Stata 13.0 being used for all data analyses. The primary study outcome is the assessment of whether CKD is a risk factor associated with COVID-19 infection, and to establish whether CKD increases the risk of severe illness in those infected with COVID-19. Secondary outcomes include mortality rates in CKD patients with COVID-19.

Results: This study approach will synthesize extant studies into a single systematic review and meta-analysis in order to establish whether or not CKD is a risk factor associated with the development of critical COVID-19 illness, and whether CKD patients are at a higher risk of being infected by COVID-19.

Conclusion: These results will provide a basis for the clinical treatment of COVID-19 in those with CKD.

Systematic Review registration: CRD42020216330 PRORPERO registration number

1. Background

After first emerging in China in late 2019, COVID-19 (coronavirus disease 2019), which is a respiratory infection that causes fever, fatigue, cough, dyspnea, and other symptoms (1), and which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (2), was declared a global pandemic by the WHO in March, 2020 (3). The SARS-CoV-2 virus has proven to be more transmissible than the SARS-CoV virus responsible for the SARS outbreak in 2003 (4), with over 40 million cases and 1 million deaths associated with COVID-19 throughout the world to date. There are no specific drugs currently available to treat COVID-19, nor has a safe and effective vaccine capable of preventing this disease yet been approved.

Chronic kidney disease (CKD) is an important and highly prevalent condition that has the potential to influence the susceptibility of populations to COVID-19. The incidence of CKD is very high, affecting over 200 million people throughout the world (5), with 2-4%, 1.8%, and 6.7% of adults in Europe, China, and the USA, respectively, suffering from stage 3-5 CKD (6). Prior evidence suggests that CKD patients are at a higher risk of COVID-19 relative to healthy individuals (7). This may be attributable to the fact that CKD patients regularly take immunosuppressive drugs, thus compromising their ability to combat novel

pathogens. A Chinese expert group has posited that patients with end-stage renal disease (ESRD) are highly susceptible to COVID-19, with infection rates as high as 16%, much higher than rates in other groups (8). Owing to their immunosuppression and abnormal physiological functionality, CKD patients are also at a higher risk of complications following COVID-19 infection (9). Given that CKD patients undergo outpatient medical visits at a relatively high frequency, they are also more likely to be exposed to COVID-19 (10). As such, there is a clear need to conduct a systematic review and meta-analysis of the relationship between CKD and COVID-19.

Within the first two months following the discovery of COVID-19 in China, 4.3% of Chinese individuals with severe COVID-19 were found to suffer from CKD (8). Due to the renal insufficiency exhibited by CKD patients, their ability to undergo treatment with certain medications is restricted, and their dosing must be tailored in an appropriate manner. One previous review found that CKD patients were excluded from approximately 50% of all registered COVID-19 clinical trials, including 52.7% of those trials testing chloroquine/hydroxychloroquine as a treatment for this disease (11). This exclusion is likely to exacerbate outcomes in CKD patients owing to a dearth of actionable clinical evidence.

Given these above factors, we believe it is essential that the association between CKD and COVID-19 be explored in depth. Our goal is to conduct a retrospective systematic review and meta-analysis in order to determine whether CKD is a risk factor associated with COVID-19 infection, and to establish whether CKD increases the risk of severe illness in those infected with COVID-19.

2. Methods

2.1 Registration

This study has applied for a registration number (CRD42020216330) on the international prospective register of systematic reviews (PROSPERO: <https://www.crd.york.ac.uk/PROSPERO/>) database. This study will be conducted as per the Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) and the Cochrane Handbook for Systematic Review of interventions guidelines.

2.2 Eligibility criteria

2.2.1 Types of studies

Cohort, cross-sectional, case-control, randomized controlled, and non-randomized controlled studies published in Chinese or English will all be eligible for inclusion in the present analysis. Studies will be excluded if they are reviews, meta-analysis, editorials, case-reports, lack relevant data, have a study size < 10, or contain overlapping datasets.

2.2.2. Participant characteristics

Study participants must meet the following criteria: 1) Patients must have been diagnosed with COVID-19 as per appropriate clinical guidelines; 2) patients must have been found to have CKD prior to COVID-19

infection; 3) patients must be > 18 years old. Patients without COVID-19 will be excluded from this study.

2.2.3. Type of intervention

No disease interventions were defined for this study.

2.2.3. Types of outcomes

Primary outcomes:

This first primary outcome will be the incidence of critical disease in analyzed patients, as defined by the occurrence of one of the following within two weeks following COVID-19 onset: 1) respiratory failure requiring manual ventilation; 2) shock; 3) combined organ failure necessitating admission to an intensive care unit (ICU). The goal of this outcome assessment will be to determine whether CKD is a risk factor for COVID-19.

The second primary outcome will be to determine whether CKD patients are more likely to suffer from COVID-19 infection. To that end, rates of COVID-19 infection among patients with and without CKD in the included studies will be compared based upon the results of reverse-transcription polymerase chain reaction (RT-PCR) tests for SARS-CoV-2 viral RNA.

Secondary outcomes:

Mortality in patients with CKD infected with COVID19.

2.3. Search strategy

Relevant articles published through November 2020 in the Wanfang, China Science Journal Citation Report (VIP database), EMBASE, CNKI, Web of Science, PubMed, and Cochrane Library databases will be incorporated into this meta-analysis. All searches will be repeated prior to the final analysis, and any relevant unpublished studies that can be identified will be incorporated as appropriate. Taking PubMed as an example, the retrieval strategy is shown in Table 1.

Table 1:

Number	Search terms
#1	"Renal Insufficiency, Chronic"[Mesh]
#2	Chronic Renal Insufficiencies[Title/Abstract]
#3	Chronic Renal Insufficiency[Title/Abstract]
#4	Chronic Kidney Insufficiency[Title/Abstract]
#5	Chronic Kidney Insufficiencies[Title/Abstract]
#6	Chronic Kidney Diseases[Title/Abstract]
#7	Chronic Renal Diseases[Title/Abstract]
#8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#9	"COVID-19"[Mesh]
#10	COVID 19 Virus Disease
#11	COVID 19 Virus Infection
#12	2019 nCoV Infection
#13	Coronavirus Disease 19
#14	2019 nCoV Disease
#15	Coronavirus Disease 2019
#16	SARS Coronavirus 2 Infection
#17	SARS CoV 2 Infection
#18	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
#19	#8 AND #18

2.4. Screening

Studies will be screened independently by two reviewers, who will eliminate duplicate and irrelevant articles. When discrepancies arise between these two reviewers, a third investigator will be consulted (Fig. 1).

2.5. Data extraction

Data will be independently extracted from included studies by two investigators. Extracted data will include: author, year of publication, study location, study type, sample size, patient age, patient medical history, intervention time, treatment plan, and follow-up time, primary variables, and primary outcomes. Data will be compiled in a standardized spreadsheet, and discrepancies will be resolved through discussion.

2.6. Risk of bias assessment

Risk of bias for the included studies will be evaluated as per the guidelines of the Cochrane Manual 5.3.0. Seven dimensions will be assessed when gauging the risk of bias, including random sequence generation, allocation concealment, blinding protocols for patients, researchers, and outcomes assessors, incomplete outcome data, selective reporting, and other sources of bias. For each of these criteria, the risk of bias will be defined as low, high, or unclear.

2.7. Data analysis

Review Manager 5.3 will be used to conduct this meta-analysis. Dichotomous data will be given as odds ratios (ORs) and risk ratios (RRs), while continuous data will be determined using weighted mean deviations (WMDs) or standardized mean deviations (SMDS).

2.8. Assessment of heterogeneity

P-value and I^2 statistics will be used to assess study heterogeneity, with significant heterogeneity being defined by $P < 0.01$ and $I^2 \geq 50\%$. Fixed-effects and random-effects models will be used to analyze data when heterogeneity is not and is present, respectively.

2.9. Sensitivity analysis

Sensitivity analyses will be performed to confirm the stability of our findings, owing to the potential for differences in methodological quality among the included studies. Multiple tests will be performed as appropriate, and studies with a high risk of bias will be excluded in these analyses to evaluate their impact on overall study findings.

2.10. Reporting bias assessment

If more than 10 studies are included in our final analysis, funnel plots will be used to gauge the risk of reporting bias. When these plots appear asymmetric, we will endeavor to establish the reason for this outcome.

3. Discussion

Prior research has identified CKD as a risk factor associated with an increased risk of severe COVID-19 infection (12), and as an independent risk factor linked to patient mortality (13)(14)(15). Renal insufficiency, as defined by an increase in baseline eGFR, serum creatinine, or serum urea nitrogen levels, is directly linked to COVID-19 mortality such that individuals with an eGFR < 60 ml/min/1.73m² were more likely to die from this disease (16)(17)(18). Age and comorbidities such as CKD have also been identified as potential risk factors linked to the incidence of adverse outcomes (19)(20)(21).

COVID-19 patients often exhibit renal failure upon hospital admission (22), with one meta-analysis having detected acute kidney injury (AKI) in 9.87% of COVID-19 patients, making this the most common form of complication after those of the respiratory and cardiovascular systems (23). One study of contemporaneous cohorts of hospitalized patients with and without COVID-19 found that AKI was more common in the former patients (56.9%) relative to the latter (37.2%), with the risk of death being three times higher in COVID-19 patients with AKI relative to those without AKI. Patients with AKI infected by COVID-19 are also more likely to report a history of prior CKD relative to patients without AKI (24).

SARS-CoV2 is able to utilize the human ACE2 protein as a receptor to infect target cells (25). As ACE2 is expressed at high levels in the kidneys, COVID-19 can readily cause acute or chronic kidney damage (23). Proximal tubule injury, endodermatitis, and SARS-CoV-2 RNA have all been detected in postmortem renal samples from patients with severe COVID-19 (26). SARS-CoV-2 can also disrupt normal renal production of erythropoietin and vitamin D and impair blood pressure regulation (27). CKD can also cause these complications, and COVID-19 infection may further lead to their exacerbation. Together, these findings strongly suggest that COVID-19 may directly damage the kidneys of affected patients, and kidney failure and death are accelerated by COVID-19 infection in those with a history of CKD (14).

These results, however, are not universal. For example, one study of 116 COVID-19 patients in the People's Hospital of Wuhan University revealed that AKI was no more common in those with COVID-19, and determined that this disease did not exacerbate AKI or CKD in affected patients. However, this study was limited by its small sample size and by the fact that it included just five patients with a history of CKD (28).

Based upon these prior studies, we believe that there is likely to be a close relationship between CKD and severe COVID-19 infections. We therefore plan to study this relationship in detail. The results of this analysis will enable clinicians to better assess the prognosis of CKD patients affected by COVID-19, and will ensure that these clinicians remain cognizant of CKD history when evaluating COVID-19 patients.

4. Declarations

4.1 Ethics and dissemination

As this is an analysis of secondary data, ethical approval is not required for the present systematic review and meta-analysis. The results of this study will be disseminated through international peer-reviewed journals

4.2 Consent for publication

Not applicable

4.3 Data availability statement

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

The data used to support the findings of this study are included within the article

The data used to support the findings of this study are included within the supplementary information files.

4.4 Competing interests

None

4.5 Acknowledgments and Funding

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References

1. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. 2020;382(18):1708–20.
2. Ge H, Wang X, Yuan X, Xiao G, Wang C, Deng T, et al. The epidemiology and clinical information about COVID-19. *Eur J Clin Microbiol Infect Dis*. 2020;39(6):1011–9.
3. Muniyappa R, Gubbi S. COVID-19 pandemic, coronaviruses, and diabetes mellitus. *Am J Physiol - Endocrinol Metab*. 2020;318(5):E736–41.
4. Ahn DG, Shin HJ, Kim MH, Lee S, Kim HS, Myoung J, et al. Current status of epidemiology, diagnosis, therapeutics, and vaccines for novel coronavirus disease 2019 (COVID-19). *J Microbiol Biotechnol*. 2020;30(3):313–24.
5. Vos T, Abajobir AA, Abbafati C, Abbas KM, Abate KH, Abd-Allah F, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. *Lancet*. 2017;390(10100):1211–59.
6. Jager KJ, Fraser SDS. The ascending rank of chronic kidney disease in the global burden of disease study. *Nephrol Dial Transplant*. 2017;32(February):ii121–8.
7. Abrishami A, Khalili N, Dalili N, Tabari RK, Farjad R, Samavat S, et al. Clinical and radiologic characteristics of covid-19 in patients with ckd. *Iran J Kidney Dis*. 2020;14(4):267–77.
8. COVID-19 therapeutic options for patients with kidney disease. 2020;(January).
9. Fu Di, Yang B, Xu J, Mao Z, Zhou C, Xue C. COVID-19 Infection in a Patient with End-Stage Kidney Disease. *Nephron*. 2020;144(5):245–7.

10. Ikizler TA, Kliger AS. Minimizing the risk of COVID-19 among patients on dialysis. *Nat Rev Nephrol* [Internet]. 2020;16(6):311–3. Available from: <http://dx.doi.org/10.1038/s41581-020-0280-y>
11. Dr RM, Selvaskandan H, Makkeyah YM, Hull K, Kuverji A, Graham-Brown M. The exclusion of patients with CKD in prospectively registered interventional trials for COVID-19—a rapid review of international registry data. *J Am Soc Nephrol*. 2020;31(10):2250–2.
12. Delfino VDA, Nascimento MM do, Barros Neto J de R, Delfino VDA, Nascimento MM do, Barros Neto J de R. Informações para pacientes com doença renal crônica pré-dialítica sobre Covid-19 (infecção pelo SARS-CoV-2). *Brazilian J Nephrol* [Internet]. 2020;42(2 suppl 1):12–4. Available from: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0101-28002020000500012&tlng=en
13. Marco LD, Ortiz A, Gimenez-civera E, Gorris L, Valencia U De. Coronavirus disease 2019 in chronic kidney disease. *Clin Kidney J*. 2020;13(3):297–306.
14. Salinas-Escudero G, Carrillo-Vega MF, Granados-García V, Martínez-Valverde S, Toledano-Toledano F, Garduño-Espinosa J. A survival analysis of COVID-19 in the Mexican population. 2020;1–8.
15. Portolés J, Marques M, López-Sánchez P, de Valdenebro M, Muñoz E, Serrano ML, et al. Chronic kidney disease and acute kidney injury in the COVID-19 Spanish outbreak. *Nephrol Dial Transplant*. 2020;35(8):1353–61.
16. Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney Int* [Internet]. 2020;97(5):829–38. Available from: <https://doi.org/10.1016/j.kint.2020.03.005>
17. Trabulus S, Karaca C, Balkan II, Dincer MT, Murt A, Ozcan SG, et al. Kidney function on admission predicts in-hospital mortality in COVID-19. *PLoS One* [Internet]. 2020;15(9 september):1–14. Available from: <http://dx.doi.org/10.1371/journal.pone.0238680>
18. Xie J, Wu W, Li S, Hu Y, Hu M, Li J, et al. Clinical characteristics and outcomes of critically ill patients with novel coronavirus infectious disease (COVID-19) in China: a retrospective multicenter study. *Intensive Care Med*. 2020;46(10):1863–72.
19. Guqin Zhanga, 1, Chang Hub, 1, Linjie Luoc, 1, Fang Fangd, Yongfeng Chene JL, Zhiyong Pengb HP. 10x20x3x5ECMO) Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's publi. 2020;(January).
20. Wang Z, Ye D, Wang M, Zhao M, Li D, Ye J, et al. Clinical Features of COVID-19 Patients with Different Outcomes in Wuhan: A Retrospective Observational Study. *Biomed Res Int*. 2020;2020:2138387.
21. Kunutsor SK, Laukkanen JA. Renal complications in COVID-19: a systematic review and meta-analysis. *Ann Med* [Internet]. 2020;52(7):1–9. Available from: <https://doi.org/10.1080/07853890.2020.1790643>
22. Uribarri A, Núñez-Gil IJ, Aparisi A, Becerra-Muñoz VM, Feltes G, Trabattoni D, et al. Impact of renal function on admission in COVID-19 patients: an analysis of the international HOPE COVID-19 (Health Outcome Predictive Evaluation for COVID 19) Registry. *J Nephrol* [Internet]. 2020;33(4):737–45. Available from: <https://doi.org/10.1007/s40620-020-00790-5>

23. Vakili K, Fathi M, Pezeshgi A, Mohamadkhani A, Hajiesmaeili M, Rezaei-Tavirani M, et al. Critical complications of COVID-19: A descriptive meta-analysis study. *Rev Cardiovasc Med*. 2020;21(3):433.
24. Hassanein M, Radhakrishnan Y, Sedor J, Vachharajani T, Vachharajani VT, Augustine J, et al. COVID-19 and the kidney. *Cleve Clin J Med*. 2020;87(10):619–31.
25. Djomkam ALZ, Olwal CO, Sala TB, Paemka L. Commentary: SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Front Oncol*. 2020;10(August):1–3.
26. Meijers B, Hilbrands LB. The clinical characteristics of coronavirus-associated nephropathy. *Nephrol Dial Transplant*. 2020;35(8):1279–81.
27. Rabb H. Kidney diseases in the time of COVID-19: Major challenges to patient care. *J Clin Invest*. 2020;130(6):2749–51.
28. Wang L, Li X, Chen H, Yan S, Li D, Li Y, et al. Coronavirus disease 19 infection does not result in acute kidney injury: An analysis of 116 hospitalized patients from Wuhan, China. *Am J Nephrol*. 2020;51(5):343–8.

Figures

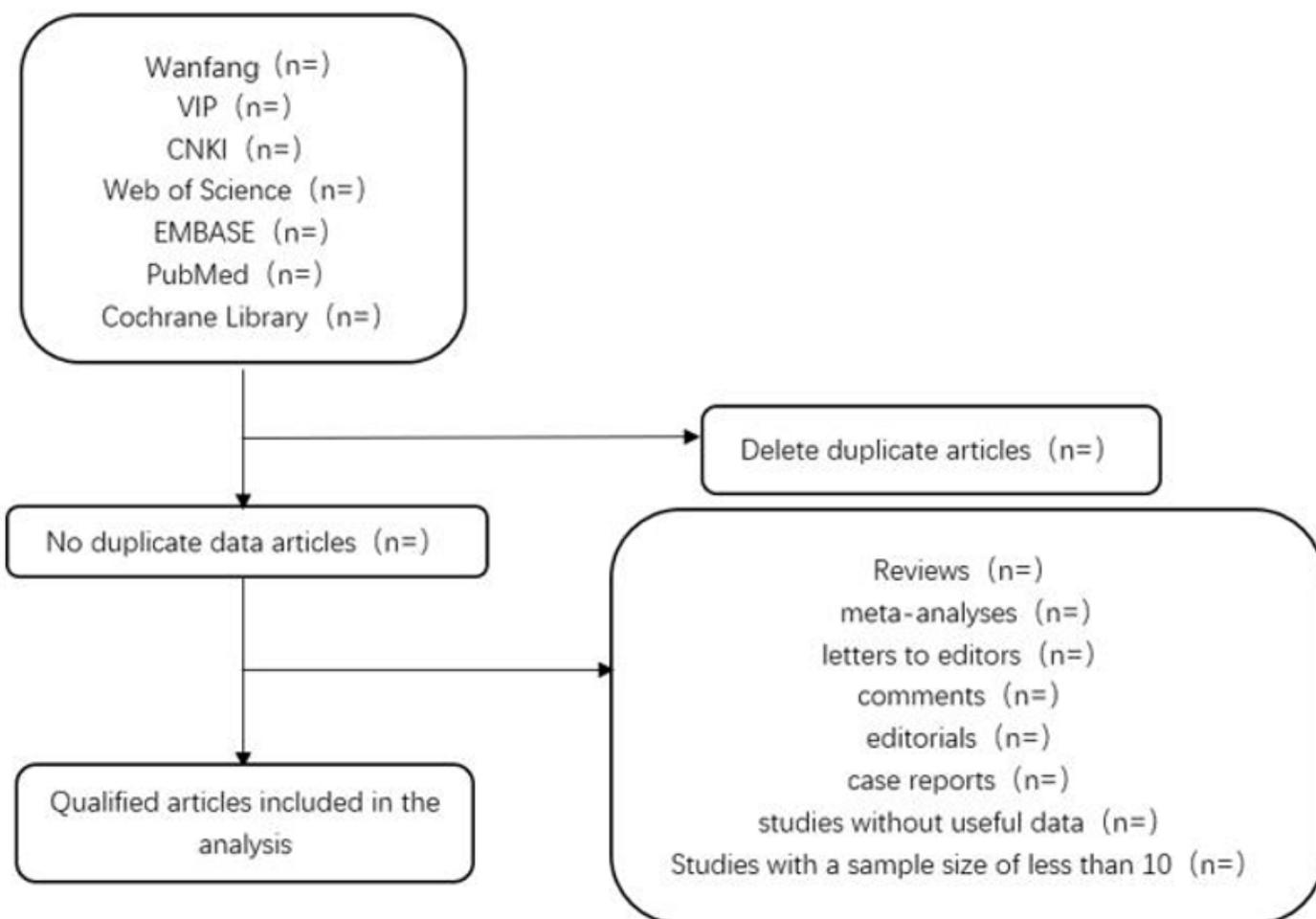


Figure 1

Flow chart

Supplementary Files

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