Efficacy and Safety of ACEIs/ARBs in Patients with COVID-19 Combined with Chronic Kidney Disease: a Protocol for Systematic Review and Meta-analysis

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Protocol

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Abstract

Background: Despite the control measure taken against the coronavirus disease 2019 (COVID-19) at global level, the pandemic has started to rebound and transmitted rapidly worldwide due to the delta strain. This strain is more virulent than the original severe acute respiratory syndrome coronavirus 2 virus. The approved vaccines or drugs can reduce mortality; still various efforts are being made to seek a complete cure. Currently, it remains controversial whether angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs) are useful in managing COVID-19 patients having comorbidities like chronic kidney disease (CKD). Evidence concerning the application of ACEIs/ARBs needs to be established through advanced meta-analyses and systematic reviews.

Methods/design: This study is designed following the PRISMA (Preferred Reporting Items of Systematic Reviews and Meta-Analyses). The studies published from December 1, 2019, to August 31, 2021 will be considered. The primary databases such as Cochrane Library, MEDLINE, EMBASE, and Chinese Biomedical Literature Database will be included, and meeting records and grey literature databases will be retrieved to compare at least two terminations or discontinued ACEIs or ARBs in clinical intervention studies. The primary results will include kidney function biomarkers, blood pressure, and long-term mortality or hospital admission severity. Pairwise random effects and meta-analyses will be performed for the selected literature using RevMan (V.5.3). The bias risk evaluation, heterogeneity, consistency, transitivity, and evidence quality will be followed as described in the Cochrane Handbook for Systematic Reviews of Interventions suggestions.

Discussion: This review will use a structured and effective method to analyze the effectiveness and security of ACEIs and ARBs in treating COVID-19 patients with CKD. Research results can present valuable evidence for patients, clinicians, researchers, or decision-makers.

System review: PROSPERO registration number CRD42021268701.

Background

Description of the condition

The angiotensin-converting enzyme 2 (ACE2) is capable of prohibiting activation of the renin-angiotensin-aldosterone system (RAAS) and acts as a crucial functional receptor for severe acute respiratory syndrome coronavirus (SARS-CoV)-2 and the coronavirus disease (COVID-19) pandemic⁽¹⁾. Selective preclinical research has proved that the expression of ACE2 is up-regulated by angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEIs and ARBs), i.e., RAAS inhibitors, triggering responses to security among patients with COVID-19⁽²⁾.

On the contrary, observations indicate an association between ACEIs or ARBs and better prognosis among patients with COVID-19. Thus, ACEIs or ARBs are anticipated to mitigate acute lung injury and

avoid angiotensin II-mediated lung permeability, inflammation, and fibrosis^(3, 4). The impacts of ACEIs and ARBs on COVID-19 have conflicting mechanistic hypotheses and observations⁽⁵⁾.

RAAS plays vital physiological functions in the homeostasis of the cardiovascular and urinary systems⁽⁶⁾. A hypothesis claims that ARB's application may augment ACE2 expression leading to the hypothesis that patients using AEBs may be more susceptible to SARS-CoV-2, which has an affinity for the enzyme ⁽⁷⁾. In contrast, another hypothesis suggests ACE inhibitors or ARBs are beneficial to COVID-19. According to this hypothesis, the use of these drugs could elevate the angiotensin 1-7 generation and lower the angiotensin II generation through the activation of ACE2 and Mas receptors, possibly playing a role in reducing inflammation and pulmonary fibrosis^(8, 9). Therefore, the ARBs and ACEIs appear to be double-edged swords in the treatment of COVID-19. Given that it is impossible to obtain valid estimations about comparative efficacy through observational studies, clinical questions should be addressed in randomized clinical trials^(10, 11).

ACEIs and ARBs are used widely as antihypertensives⁽¹²⁾ for treating renal fibrosis and reduce proteinuria in various kidney diseases⁽¹³⁾. However, considering the impact that ACEIs and ARB may have on the deterioration of renal function, it is recommended to discontinue the use of ACEIs/ARBs during some clinical conditions, such as hyperkalemia, bilateral renal artery stenosis, and significant elevation of serum creatinine⁽¹⁴⁾. However, it is unclear whether the impact of ACEIs or ARBs on clinical outcomes are positive, neutral, or negative in COVID-19 patients combined with CKD, whether ACEIs or ARBs affect the progression of renal failure in COVID-19 infection caused by CKD, and whether ACEIs or ARBs among patients with CKD have an impact on the high COVID-19 infection risk. Does the treatment using ACEIs or ARBs affect the progression of renal failure in COVID-19 infection causing renal damage?

Description of the intervention

ACEIs/ARBs remedy of dose not limited.

ACEIs/ARBs placebo or standard care.

Why it is significant to implement this review

The SARS-CoV-2-caused COVID-19 infection is spreading worldwide. ACEIs and ARBs have been controversial in treating COVID19⁽¹⁵⁾, particularly in severe or combined kidney damage cases. Systematic review and meta-analysis on its validity and security are of great significance. Under the systematic review protocol, merely randomized controlled trials (RCTs) in COVID-19 treatment were completely examined and elucidated, without any language or publication restriction. The research provides a good reference for patients, clinicians, researchers, and policy decision-makers focusing on ACEIs and ARBs validity and security in COVID-19 combined with CKD.

Objective

This study aimed to (1) determine whether there is any change in the withdrawal and further medication with ARBs or ACEIs for the COVID-19 patients having CKD, (2) assess the validity and security evidence for ACEIs or ARBs in treating COVID-19 through a systematic meta-analysis of randomized studies.

Methods/ Design

The protocol is established based on the PRISMA protocols ⁽¹⁶⁾. This systematic review can be found in the PROSPERO database (CRD42021268701, on [http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID = CRD42021268701](http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42021268701)). Synchronous updates for amendments in the protocol or review process were performed in PROSPERO registration. Enforcement and reporting for the systematic review will observe the Cochrane Handbook for Systematic Reviews of Interventions and Suggestions, and the extended PRISMA statement for reporting systematic reviews containing interventions based on meta-analyses ^(17, 18).

Criteria for considering studies for this review

Types of studies

Only RCTs (random, non-blinded, placebo) were considered. Due to false-negative (type II) errors, RCTs do not possess sufficient statistical capacity to assess safety outcomes that are atypical or rare ⁽¹⁹⁾. Other research types, such as observational research, case series, or case reports, were omitted ⁽²⁰⁾.

Types of participants

Patients diagnosed with CKD and COVID-19, regardless of whether they had CKD before COVID-19 infection or as a result of infection, are included. Patients with CKD or COVID-19 alone are excluded, with no restriction on age, sex, or course of the disease. No clinical-stage restrictions are applied to mild, moderate, or severe/critical cases. Moreover, there are no restrictions on comorbidities.

Types of interventions

Medications with ACEIs and ARBs are given to the intervention group using a random dose. There were no restrictions on standard therapy in the review (such as supportive therapy, antiviral, dialysis treatment).

Types of comparator(s)/control

The control group received the same treatment during the original research. No restrictions were proposed for standard therapy.

Types of outcome measures

Primary outcomes

Primary endpoints

- Time of clinical recovery
- Blood pressure
- Blood creatinine fluctuation,
- Urine protein fluctuation;
- eGFR fluctuation.

Secondary outcomes

Secondary endpoints.

- Discharged date.
- All-cause mortality.
- Frequency of respiratory.
- Oxygen saturation
- Treatment of emergency adverse events

Search methods for identification of studies

E-databases, including PubMed, Embase, CENTRAL, the Chinese Biomedical Literature Database, CNKI, VIP, and Wanfang, are searched between December 1, 2019 to August 31, 2021, in English and Chinese languages. Additionally, Google and Baidu Scholar are employed for seeking potential missing articles. For providing high-quality evidence, RCTs papers were included exclusively.

Reviewers will use the combinations of the following terms for electronic searches: severe acute respiratory syndrome coronavirus 2, novel coronavirus, SARS-CoV-2, COVID-19, COVID19, 2019-nCoV,

chronic kidney chronic disease, chronic renal disease, chronic kidney failure, chronic renal failure, chronic kidney injury, randomized controlled trial, randomized, randomly, trials. Table 1 demonstrates the PubMed search strategy, which may be modified by reviewers based on the requirements of other databases

Table 1.

Data collection and analysis

Selection of studies

Screening, trial selection, and data extraction are carried out separately by two reviewers. All searched studies were imported into EndNote X10 to screen titles and abstracts and exclude duplicates and studies inconsistent with inclusion criteria. Finally, the inclusion of studies is decided when reviewers read the whole text of the remaining articles. Making contact with the original corresponding authors is required when access to text is unavailable. The third reviewer is responsible for arbitrating the discrepancies. For summarizing the research selection process, the PRISMA flow chart is displayed (Figure 1).

Data extraction and management

Two reviewers implement the pre-designed data collection process to retrieve information from chosen studies, including reference ID independently; author information; publication year; research type; research design; research setting; sample size; participant characteristics (age, sex, disease duration and severity, laboratory test, CT scan); ACEIs and ARBs intervention and control groups (details about randomization, blinding, allocation, intervention methods, and durations) and primary and secondary outcomes at reporting time points. The third reviewer is responsible for solving the inconsistency. Data are cross-checked before transfer.

Assessment of risk of bias in included studies

The Cochrane Risk of Bias Assessment Tool is applied by two assessors for evaluating publication bias risk in enrolled studies from eight research fields, including generation of randomization sequences, random allocation concealment, participant/personnel/outcome assessor blinding, insufficient outcome data, the bias of selective reporting, as well as other biases. Each field was categorized as high, unclear, or low bias risk. As to unclear division, contact with original corresponding authors is necessarily required. The third scrutator is responsible for solving the inconsistency⁽²¹⁾.

Measures of treatment effect

Synthesis and statistical processing of efficiency-related data are accomplished with RevMan V.5.3 independently. As to binary data, a risk/odds ratio with 95% confidence intervals (CIs) was used, while in the case of continuous data, a mean difference/standardized mean difference (SMD) plus 95% CI were adopted. Different assessment tools were applied in conjunction with SMD.

Dealing with missing data

Making a contact with original corresponding authors through mail or telephonically was necessarily required in case of any unclarity or non-availability of data. If the problem remains pending, the studies are excluded. For addressing the underlying influences of missing data, the sensitivity analysis is performed^(22, 23).

Assessment of clinical and methodological heterogeneity

For statistical heterogeneity assessment, the χ^2 and I^2 statistic tests are performed. In the case of low heterogeneity ($I^2 < 50\%$), the fixed-effects model is adopted, whereas the random-effects model is employed for moderate heterogeneity ($50\% < I^2 < 75\%$). Meta-analysis is not required in the condition of significantly high heterogeneity ($I^2 > 75\%$).

Assessment of reporting biases

Where 10~ eligible trials are enrolled, the underlying bias of reporting is assessed by funnel plotting. In addition, Egger regression and Begg correlation tests are required to recognize asymmetry in the funnel chart⁽²⁴⁾.

Data synthesis

Following Cochrane guidelines, in case of low heterogeneity of the pooled data, the fixed-effects model is adopted. Where the heterogeneity was moderate, the random-effects model was employed. Meta-regression or subgroup analysis-based determination of underlying sources is done, when the heterogeneity is high. A p-value of < 0.05 represented statistical significance. The results are presented as diagrams when the meta-analysis is impossible⁽²⁵⁾.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were conducted where feasible concerning the severity/duration of disease, administration route, as well as source and dosage of ACEIs/ARBs, for elucidating the heterogeneity.

Sensitivity analysis

Sensitivity analysis was performed where feasible for robustness evaluation of the joint effects in enrolled trials, subject to variables, including the sample size, methodological quality, data deficiency, and high bias risk.

Summary of evidence

The present review classified the evidence quality into very low, low, moderate, and high levels in accordance with the GRADE approach by the Cochrane Collaboration Network ^(26, 27). Evidence quality in specific studies was evaluated by the bias risk, indirectness, inconsistency, publication bias, imprecision, dose-response relation, as well as effect size. The survey results are compiled in the “Summary of surveying table.” Any inconsistency was addressed through negotiation or arbitration by the third examiner.

Patient and public involvement

Since this research was performed through a systematic review of published literature, no patient or the public was involved in the design and implementation of research, data analysis, or result dissemination.

Ethics and dissemination

The present systematic review was based on published data, so ethical approval was exempted. The results are scheduled to be published at international conferences, which are also available in peer-reviewed journals.

Discussion

Viruses keep altering and evolving in nature, similar to other species. The worldwide outbreak and diffusion of COVID-19 or delta variant-COV are a huge challenge to human survival. Therefore, ACEIs/ARBs drugs appear particularly significant owing to the prominent effects in regulation, multi-system, anti-fibrosis, and multi-organ protection functions^(3, 4). However, there is controversy due to the lack of high-quality evidence⁽⁹⁾. The top priority currently is to decide the validity and security of ACEIs/ARBs against inflammatory infection process, renal fibrosis progression, or multiple organ complications.

This meta-analysis will use a structured and effective method to analyze the effectiveness and security of ACEIs and ARBs in treating COVID-19 patients with CKD. Research results can present valuable evidence for patients, clinicians, researchers, or decision-makers. The review comprises identification,

research inclusion, data extraction, and data synthesis. If any modification is required, we will mark the changes and reasons on the date of each modification. For the ongoing studies, the meta-analysis will update the latest data in randomized studies.

Strengths and limitations of this study

It is necessary to incorporate PRISMA into the systematic review protocol. It is well-established that the current systematic review evaluates the validity and security of ACEIs and ARBs in treating COVID-19 patients with kidney diseases for the first time. The study aims to perform a systematic review of quantitative data from different medical databases and deeply interpret the efficacy and security of ACEIs or ARBs for COVID-19 patients with kidney diseases. The primary limitations of this study are the possibilities of inconsistent and poor quality of reports, publication bias, and methodological quality of gray literature. In addition, whether RCTs can be accomplished to gather sufficient patient data for elucidation and conclusions is also a limitation.

Abbreviations

ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers; CKD: chronic kidney disease; COVID-19: Corona Virus Disease 2019; COV: Corona Virus; ID: Identity document; **RCTs: randomized controlled trials**; MD: Mean differences; EMBASE: Excerpta Medica Database; MEDLINE: Medical Literature Analysis and Retrieval System Online; PRISMA: Preferred reporting items for systematic review and meta-analysis; PRISMA-P: Preferred reporting items for systematic review and metaanalysis—protocols; PROSPERO: International Prospective Register of Systematic Reviews; RR: Risk ratio; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; SD: Standard deviation; SMD: Standardized mean difference.

Declarations

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

JX, SR and JF provided the initial idea for this research. SR, XM and XL proposed and revised the preliminary idea of the search strategy. JX, NM and JF participated in the design of research. NM, XM and SR were consulted on clinical decisions. JX, XL and SR contributed to the initial draft. NM, XM and JF were responsible for revising the draft. All authors approved the final work before submission.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Additional data of the research could be provided upon request E-mails to the corresponding author.

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Table

Due to technical limitations, table 1 is only available as a download in the Supplemental Files section.

Figures

Image not available with this version

Figure 1

PRISMA flow chart

Supplementary Files

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- [Table1SearchstrategyforthePubMeddatabase.docx](#)