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PREDICTION OF MORTALITY IN HYPERTENSIVE COVID-19 PATIENTS RECEIVING RENIN ANGIOTENSIN ALDOSTERONE-BASED THERAPY: AN EVIDENCE-BASED CASE REPORT

Azis Muhammad Putera,[1] Fahira Yusriya,[1] Mariska Andrea Siswanto,[1] Ugiadam Farhan Firmansyah,[1] Umar,[1] Melva Louisa [2*]

[1] Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia
[2] Department of Pharmacology and Therapeutics, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

*melva.louisa@gmail.com

Abstract

Hypertension is the most common comorbidity found in COVID-19 patients, which might increase the risk of mortality. Inhibitors of the RAAS are among the first-choice agents in hypertension, including ACE-I and ARB. The use of RAAS inhibitors is thought to increase the expression of ACE-2 receptors, facilitating the entry of SARS-CoV-2, which might result in increased mortality, though previous studies got conflicting results. This evidence-based case report was made to answer whether the use of RAAS inhibitors increases the mortality in COVID-19 patients.

We explored studies relevant to our clinical question, including only systematic reviews, meta-analyses, and cohort studies that compared mortality rate in hypertensive COVID-19 patients receiving RAAS inhibitors to those who were not. Articles were then selected by title and abstract screening and elimination of articles that did not fit our clinical question and eligibility criteria. The result of selected papers was then critically appraised according to the validity, importance, and applicability of the studies using the critical appraisal form from CEBM.

From 191 articles initially found, three studies fit our eligibility criteria (1 systematic review, evidence level 2A, and two cohort studies, evidence level 2B). The systematic review shows an OR of 0.73 ((95% CI 0,56-0,95; p = 0.001) with substantial heterogeneity (I^2=74%). The first cohort study shows an HR of 0,97 (95% CI 0,89-1,06) in patients receiving ACE-I and HR of 0,98 (95% CI 0,89-1,06) in patients receiving ARB compared to those who received CCB. The second cohort study shows an OR of OR: 0.623 (95% CI 0.423-0.917; p = 0,016).

Findings gathered from various studies showed inconclusive results regarding the use of RAAS inhibitors in hypertensive COVID-19 patients. From our critical appraisal, we found that RAAS inhibitors' usage tends not to increase the mortality of COVID-19 patients. Thus, we suggest that COVID-19 patients on RAAS inhibitors should continue with their treatment regimen. A large-scale cohort study is still needed to get a conclusion with more robust evidence.

Keywords: *SARS-CoV-2, ACE-2 receptors, ACE inhibitors, Angiotensin receptor blockers, Prognosis*

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious respiratory disease caused by *severe acute respiratory syndrome Coronavirus* 2 (SARS-CoV-2). The number of confirmed cases worldwide as of December 20, 2020, was 75,479,471 cases with 1,686, 267 deaths.[1] The manifestations of COVID-19 vary widely, ranging from asymptomatic patients, mild cases, moderate cases with mild pneumonia, severe cases with severe pneumonia, and critical cases with acute respiratory distress syndrome.[2-3] The elderly and people with comorbidities like hypertension, cardiopulmonary disorders, and diabetes are people at increased risk for severe outcomes and death due to COVID-19.[4-6] Hypertension is the most common comorbidity in COVID-19 patients, including in Indonesia (52,1%).[4] COVID-19 patients with hypertension have a higher risk of death than those with normal blood pressure. Thus, special attention should be given to this population.[5]

The renin-angiotensin-aldosterone inhibitors are groups of drugs which include the angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), known as the first-line agent of choice in the pharmacotherapy of hypertension.[6] The use of RAAS inhibitors in patients with COVID-19 remains a controversial issue. Some animal studies have shown that ACEIs and ARBs upregulate the expression of ACE2 in various organs. This might potentially aggravate and increases the risk of death in COVID-19 patients, though the upregulation of pulmonary ACE2 in humans remains unproven.[7] Interactions between SARS-CoV-2 spike protein and ACE2 receptors with the TMPRSS2 protease facilitate the entry of SARS-CoV-2 into a host cell.[8] Observational studies showed conflicting results. The use of ACEI/ARB was associated with an increase in mortality rate and might be a predictor of in-hospital death.[9] At the same time, other studies found that the use of ACEI/ARB did not increase the mortality rate.[10] This evidence-based case report was made as an effort to answer whether the use of RAAS inhibitors increases the in-hospital mortality rate of COVID-19 patients.

Case

A 40-year old male with a history of hypertension came to the clinic with a dry cough, fever, and breathing difficulty. The patient had been in contact with a confirmed case of COVID-19. Further examinations gathered the following data: blood pressure 124/82 mmHg, the body temperature of 38,5^{o}C, respiratory rate 32x/min, heart rate 116x/min, and oxygen saturation of 88%. Due to the low oxygen saturation and breathing difficulty, the patient underwent a nasopharyngeal swab for PCR test and then admitted to the hospital. The patient had a history of hypertension in the last six years and routinely consumed an ACE-inhibitor drug, captopril 3x25 mg per day. The patient had never complained about the current symptoms before. Some studies showed that the usage of RAAS inhibitors might upregulate the expression of ACE-2 receptors, potentially facilitating the further entry of SARS-CoV-2 into its host cells and aggravating the disease severity.

Methods

Search strategy

We used several search engines to find relevant articles (PubMed, Scopus, and Cochrane (EMBASE)) based on keywords listed in Table 1. To increase sensitivity, we used the Boolean Operator "OR,"whereas the Boolean Operator "AND" was used to improvethe specificity of our searching method. Duplications were removed for further selection using the predetermined inclusion and exclusion criteria. Details regarding the search strategy for journals in the database can be seen in Table 1

Selection Criteria

The selection criteria were based on inclusion and exclusion criteria. The initial search did not use a language filter, but for the selection process, the authors only assessed articles written in English. After entering keywords with the help of Boolean operators, 203 journals were found. There were 12 duplicate articles found; 191 journals were then selected for the title and abstract screening process according to our clinical question, resulting in 22 journals selected for critical appraisal.

Eligibility Criteria

The accepted study design was prognostic in the forms of systematic reviews and meta-analyses of cohort studies and prospective and retrospective cohort studies in Indonesian and English. The targeted population of this study was hypertensive adult patients (aged >18 years) with a confirmed diagnosis of COVID-19 who routinely took RAAS-inhibitors. Therapy with RAAS inhibitors such as renin inhibitors, ACE inhibitors, or angiotensin receptor blockers was deemed the "exposure" in our clinical question, aiming to assess whether the use of RAAS inhibitors affects the mortality of hypertensive COVID-19 patients.

Critical appraisal

selected journals were evaluated by all Authors. The assessment tool in the prognostic study used by the authors was the University of Oxford 2010 CEBM (Center for Evidence-based Medicine).[11]

Results

We found 22 articles consisting of 7 systematic reviews and 15 observational research articles (prospective/ retrospective cohort studies) to be critically appraised. Of the seven systematic reviews found, the most recent one, which has included manuscript in previous systematic reviews and fulfills the appraisal criteria, was included in the final report (systematic review by Hasan et al, 2020.[12] From the critical review process on observational research articles, there were only two articles that we had in the final report after appraisal (studies by Trifiro et al.[13] and Negreira-Caamano et al[14]. The journal search strategy is provided in be seen in the flowchart below (**Figure 1**).

Table 2 provides a summary of the main findings of the three selected studies. The results of the critical review of the systematic review are shown in **Table 3**, while **Table 4** showed the results of the cohort study appraisal.

The first study that meets the criteria of validity, importance (*importance*), and applicability is a systematic review and meta-analysis by Hasan et al. (2020). The study performed a multivariate analysis of 24 prospective and retrospective cohort studies with statistical adjustments to see the relationship between ACE inhibitors and ARBs and mortality in COVID-19 patients with a history of hypertension. The eligibility criteria for this study were cohort observational studies that observe the use of ACE inhibitors and ARBs in COVID-19 patients. This is reasonable considering that COVID-19 infection has only occurred in 2020, so that no studies with prospective cohort designs have been conducted in a large population for a long period. We assessed that this study met the validity criteria because it included all existing studies from PUBMED, Google Scholar, SSRN, and medRxiv databases. We also evaluated the importance of these study results from the forest plot results and their applicability to patients in our clinical questions. The results of the critical appraisal of Hasan et al. article can be seen in **Table 3**.[12]

The results of Hasan et al. meta-analysis are presented using a forest plot. The analysis showed that the odds ratio (OR) for mortality of COVID-19 patients who used ACEI/ ARB inhibitors compared to those who did not use ACEI / ARB had an OR value of 0.73 (95% CI 0.56-0.95) with substantial heterogeneity (I^2= 74%, p = 0.001).[12]

The second study that was conducted by Trifirò et al. 2020 was a cohort study of 42,926 COVID-19 patients with a median age of 69 years old. Several other prognostic factors that also influence mortality risk are age, gender, hospitalization in the last 12 months, Charlson index, particular drug consumption over the previous 12 and 3 months, and other comorbidities. According to the last univariate analysis, the elderly is the strongest mortality predictor with the HR 37.5 (95% CI 31.4 - 44.8). After adjusting to the potential confounding, there is no significant difference in mortality risk between ACEI users HR 0.97 (95% CI 0.89-1.06) or ARB users HR 0.98 (95% CI 0.89-1.06) compared to CCB users. This finding was confirmed through sensitivity and subgroup analysis. There is a higher mortality risk of ACEI users HR 1.12 (95% CI 1.04-1.20) or ARB users HR 1.13 (95% CI 1.06-1.21) compared to non-antihypertensive users. Although the effect on this finding almost totally disappears after conducting a multivariable analysis.[13]

The third study conducted by Negreira-Caamaño et al. (2020) was a study with a cohort design in inpatients with COVID-19. The exclusion criteria for this study were patients aged < 18 years old, had no history of hypertension, and positive

COVID-19 without respiratory distress. In a total of 1086 patients, 545 patients met the inclusion criteria, and 545 patients were excluded. Furthermore, patients were categorized based on their history of antihypertensive drug uses, 1392 patients with ACEI/ARB, and 153 patients as the non-users of ACEI/ARB. This study was conducted for eight weeks from March 3rd to April 30th 2020. The univariate results showed that patients with a history of using ACEI or ARB had a lower rate of death with an OR value of 0.623 (95%CI 0.423-0.917; p=0.016) compared to patients without ACEI or ARB prescription (30.4% vs 41.2%). Meanwhile, the multivariate analysis showed that the use of ACEI or ARB acts as a protective factor from death in hospitalized patients with an adjusted OR value of 0.550 (95% CI: 0.304 – 0.930; p = 0.047).[14]

Discussion

This report aims to address the controversy regarding the relationship between the use of RAAS inhibiting drugs such as ACE inhibitors and ARBs on the mortality rate of COVID-19 patients with hypertensive comorbidities. From our search results, there is one systematic review and meta-analysis study with high validity and two cohort studies with moderate validity. The assessment for the importance of all three studies is provided below.

Systematic review and meta-analysis of Hasan et al (2020) included 12 studies that included *Odds Ratio* (OR) that have been adjusted. The OR value indicates that the use of ACEI/ARB tends to be protective. However, it can be seen that the heterogeneity of the meta-analysis is substantial, making it difficult to draw conclusions. This study states that before a prospective cohort study or randomized control trial with a large population prove the harmful use of ACEI/ARB in COVID-19, patients are recommended to continue treatment with ACEI / ARB because it is protective and reduces patient mortality.[12]

Trifirò G et al. 2020 reported no higher mortality risk of using ACEI/ARB compared to CCB among COVID-19 patients.[13] This finding accords with the previous systematic review and meta-analysis study which prove no higher mortality risk of protective effect on using RAAS inhibitor compared to other antihypertensive drugs among COVID-19 patient.[15]

Negreira-Caamaño M et al. (2020) implies that the use of ACEI or ARB does not show a greater risk of mortality in hospitalized patients compared to patients without ACEi or ARB prescription. The protective results of using ACI/ARBD as a treatment can even be associated with reducing the prognosis in patients COVID-19 with hypertension.[14] The protective factor of ACEI or ARB was also mentioned before in the previous study conducted by Gao C (2020), where these treatments' use provides a beneficial effect in hypertensive patients in Asia.[16]

Hasan et al (2020) study has several advantages and disadvantages. The advantage of this systematic review is that this study includes many original studies from various countries in America, Europe, and Asia without any language limitations. The drawbacks are that of the 24 studies included only two are of high quality, while the rest are of medium quality. Also, the meta-analysis heterogeneity in this study was substantial, making it difficult to conclude.[12]

A study by Trifirò G et al. (2020) has several strengths. This study is an immense scale cohort study in Italy. The sample selection of the study was conducted transparently and explained clearly. The researchers analyzed numerous prognostic factors that might be confounding the study. They also conducted sensitivity and subgroup analysis. On the other hand, this study has several weaknesses. This study design is retrospective, which could not evaluate the outcome over time. There is a possibility of exposure misclassification, mainly about the cessation of antihypertensive consumption or switching the drug due to COVID-19. In this study, there is no information on obesity and smoking risk factor that might be the potential confounder. Besides, there is a possibility of selection bias because hospital admission was not defined and depend on various factors, such as the availability of beds, patient severity, etc.[13]

There are several advantages and disadvantages that can be seen in Negreira-Caamaño M et al. (2020) study. The advantage is that the time taken to follow-up form onset, and the outcome was using the CDC recommendations. The

researchers also made adjustment to all the risk factors and comorbidities that might act as the confounding factors in this study. The data of daily follow-up was also provided. However, there are some weaknesses that can be found in this study, such as not paying attention to the effectiveness of patient treatment before being admitted to the hospital and matching was not mentioned in the methods for the prognostic and comorbidities, yet the results showed an adjusted OR.[14]

The present evidence-based case report assessed several studies that had study subjects who were matched with patients in clinical scenarios. The subject in question is an adult COVID-19 patient with comorbid hypertension who is receiving RAAS inhibitor therapy. Based on the results obtained, the use of RAAS inhibitors did not increase the mortality rate for adult COVID-19 patients. The results of this case report can still support the clinical use of RAAS inhibitor therapy in COVID-19 patients. Thus, in clinical practice, the use of RAAS inhibitors for COVID-19 patients can be continued.

COVID-19 patients with a history of hypertension should continue RAAS inhibitor drug consumption when they used to take the drug regularly. However, if the patient does not have a history of taking RAAS-inhibiting drugs, this drug should not be given. Also, researchers suggest a large-scale cohort or systematic review with homogeneous subject characteristics regarding the prognosis of COVID-19 patients receiving RAAS inhibiting therapy.

Conclusion

A definite conclusion regarding the use of RAAS inhibitors for COVID-19 patients with hypertension is still uncertain. Available studies were generally low in evidence quality with heterogeneous results. Considering that this pandemic is a new phenomenon, it is perfectly understandable that investigations are still limited to varying quality levels. Even then, from what we gathered, the use of RAAS inhibitors did not tend to increase in-hospital mortality for COVID-19 patients. A large-scale cohort study is needed to get a conclusive answer with a more substantial level of evidence. Thus, it might be advantageous to continue on using RAAS inhibitors.

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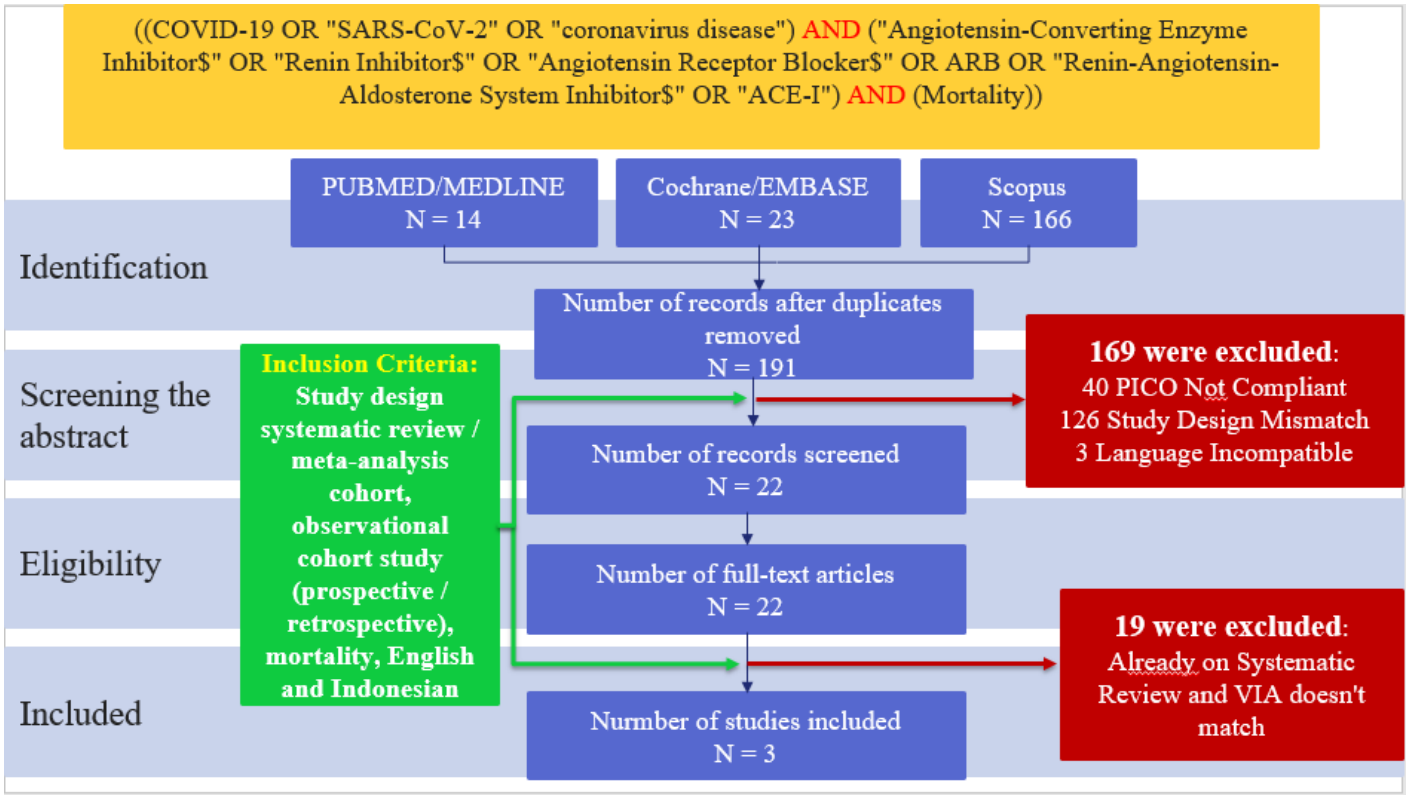

Figure 1. Flowchart of the search and selection strategy

Table 1. Terminology used in the 3 journal databases

Database	Search criteria	Hits
PubMed	Search: (((COVID-19 [Supplementary Concept]) AND (((Angiotensin-Converting Enzyme Inhibitors [MeSH] OR Aliskiren [Supplementary Concept])) OR (Angiotensin Receptor Antagonists [MeSH]]]] AND ((Mortality [MeSH Terms]))	14
Scopus	((COVID-19 OR "SARS-CoV-2" OR "coronavirus disease") AND ("Angiotensin-Converting Enzyme Inhibitor$" OR "Renin Inhibitor$" OR "Angiotensin-Aldosterone System Inhibitor$" OR "ACE-I") AND (Mortality))	166
Cochrane	(("COVID-19" OR "coronavirus") AND ("Angiotensin-Converting Enzyme Inhibitors" OR "Renin Inhibitor" OR "Angiotensin Receptor Blocker" OR Renin-Angiotensin-Aldosterone System Inhibitor") AND Mortality)	23

Table 2. Summary of Findings from the Appraised Studies

Author, Year	Location	Study Design	Age	Indicator		Comparator		Outcome	Other Prognostic Factors	Limitation	Level of Evidence
				Therapy	Mortality	Therapy	Mortality				
Hasan et al., 2020	various countries around the world	Systematic review and meta-analysis	34-86 years old	ACEI/ ARB	-	Absence of use of ACEI/ ARB	-	OR 0,73 (95% CI: 0,56-0,95)	There are multiple prognostic factors from 21 studies	Low-quality studies	2a
Trifirò G, 2020	Italy	Retrospective Cohort	69 (57-79) years old	ACEI	1606/ 4663	CCB	822/ 2178	HR 0.97 (95% CI 0.89-1.06)	Age, gender, the amount of hospitalization in the last 12 months, Charlson index, certain drug consumption in the last 12 and 3 months, and other comorbidities	No outcome over time collection data, the possibility of exposure misclassification, no information about obesity and smoking risk factor, and the possibility of selection bias	2b
				ARB	1540/ 4859	CCB	822/ 2178	HR 0.98 (95% CI 0.89-1.06)			

Negreira-Caamaño, 2020	Spain	Prospective cohort	76.5 ± 12.3 years old	ACEI/ ARB	119/392	Absence of use of ACEI/ ARB	63/ 153	OR 0.623 (95% CI 0.423-0.917; p=0,016)	Gender, Age, Diabetes, history of smoking, obesity, heart failure, lung disease, reduced LVEF, Ischemic heart disease, atrial fibrillation, CKD, active cancer	The effectiveness of patient treatment before being hospitalized is not considered, 'matching' is not mentioned for prognosis and comorbid factors, yet the results showed an adjusted OR.	2b

Table 3. Critical appraisal from included systematic review using CEBM Tools

Author, Year	Clear PICO	Relevant evidence	Include only high-quality studies	Appropriate tables and plots	OR	Hetero-geneity
Hasan et al., 2020[12]	Yes	Yes	No	Yes	0.73 (95% CI: 0.56 – 0.95) p <0.05	74%

Table 4. Critical appraisal of included cohort studies using CEBM Tools

Author, Year	Representative Sample	Sufficient follow-up	Blinding for outcome criteria	Adjustment of important prognostic factor	Validation in an independent group	Outcomes over time
Trifiro G., 2020[13]	Yes	Yes	No	Yes	Unclear	Unclear
Negreira-Caamano M, 2020[14]	Yes	Yes	No	Yes	Unclear	Yes