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Meta-Analysis

Effect of ACE Inhibitor Therapy on Mortality in COVID-19 Patients with Hypertension: Meta-Analysis

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ABSTRACT

Background: Acute respiratory syndrome Corona Virus 2 (SARS-CoV-2) can trigger the occurrence of respiratory infectious disease Coronavirus Disease 2019 (COVID-19). Patients who have comorbid health problems such as hypertension, chronic liver, cardiovascular and diabetes mellitus are more likely to experience deterioration and death. ACE inhibitor therapy in patients with hypertension has a therapeutic effect in lowering blood pressure and is able to reduce mortality rates in COVID-19 patients, but the benefits of ACE inhibitors in patients with COVID-19 are still uncertain. This study aims to determine how much influence ACE inhibitors have on COVID-19 patients with hypertension on mortality rates.
Subjects and Method: This study is a systematic review and meta-analysis with the following PICO, population: COVID-19 patients with hypertension. Intervention: administration of ACE inhibitor therapy. Comparison: therapy other than ACE inhibitors. Outcome: mortality. The articles used in this study were obtained from several online databases, including Science Direct, PubMed and Google Scholar. The keywords used in the article search were: "ACE inhibitor" AND "COVID-19" AND "Hypertension" AND "mortality". The articles included are full-text English with a cohort study design from 2020 to 2021 and report the odds ratio in multivariate analysis. The selection of articles was carried out using the PRISMA flow chart. The articles were analyzed using the Review Manager 5.4. application.
Results: A total of 4 cohort studies involving 4,998 COVID-19 patients from America, China and Italy were selected for systematic review and meta-analysis. The data collected yielded information that COVID-19 patients with hypertension who were given ACE inhibitors reduced the risk of mortality 0.67 times compared to COVID-19 patients with hypertension who were not treated with ACE inhibitors (aOR= 0.67; 95% CI= 0.36 to 1.26; p= 0.210).
Conclusion: ACE inhibitors can reduce the risk of mortality in COVID-19 patients with hypertension.

Keywords: COVID-19, hypertension, ACE inhibitors, mortality.

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BACKGROUND

Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is an infectious respiratory disease better known as Coronavirus Disease 2019 (COVID-19). COVID-19 was reported for the first time on December 31, 2019 from Wuhan, Hubei province in China. The World Health Organization (WHO) declared a pandemic for COVID-19 on March 11, 2020, immediately after meeting the epidemiological criteria (Singh et al., 2020). The clinical symptoms of

COVID-19 patients are wide ranging from asymptomatic or asymptomatic, mild symptoms, pneumonia, severe pneumonia, ARDS, sepsis, to septic shock. Approximately 80% of cases have mild or moderate conditions, 13.8% have complaints of severe illness, and about 6.1% of patients are in critical condition (Susilo et al., 2020).

Each individual has different clinical symptoms. On average, patients infected with SARS-CoV-2 have manifestations of several clinical conditions in the respiratory tract such as sneezing, coughing, shortness of breath and fever (Susilo et al., 2020). The majority of people with COVID-19 have co-morbidities such as cardiovascular, hypertension, chronic liver and diabetes mellitus. Patients who have comorbidities are most likely to experience unfavorable conditions and even death (Huang et al., 2020). The analysis has been carried out that comorbid conditions such as hypertension and diabetes mellitus, male and active smoking are risk factors for SARS-CoV-2 infection. With a dominant distribution of male sex because it is thought to be related to the large number of active smokers. Patients with a history of smoking, hypertension, and diabetes mellitus will experience an increase in ACE2 receptor expression (Susilo et al., 2020).

Hypertension is a condition in which a patient has a systolic blood pressure of more than 140 mmHg and a diastolic blood pressure of more than 90 mmHg. Non-communicable diseases (PTM) such as hypertension are very dangerous diseases (Silent Killer) (Yonata and Pratama, 2016). Hypertension is a major comorbidity in patients who are infected with SARS-CoV-2. According to recent reports in China and Singapore, 12.8% to 31.2% of patients with COVID-19 have pre-existing hypertension. The condition of these patients will eventually become more severe and more prone to death (Yang et al., 2020).

ACE inhibitors are the mainstay of therapy for hypertensive patients with complications of heart failure because they can significantly prevent the development of heart failure and reduce left ventricular hypertrophy and remodeling of blood vessel walls (Lestari et al., 2019). ACE Inhibitors have an RAA working system, namely ACE inhibitors can result in ACE unable to convert angiotensin I to angiotensin II. So that due to high blood pressure causes enlargement of the left ventricle of the heart (Left Ventricular Hypertrophy). This condition causes complications of hypertension, namely myocardial infarction. The Renin Angiotensin Aldosterone/RAA system has a role in hypertension. In the RAA system, which plays an active role in sympathetic stimulation, it can cause sodium retention, resulting in an increase in blood volume. Pharmacotherapy in hypertension is to intervene with the RAA system with ACE inhibitors (Jiofansyah, 2020). Treatment of patients with hypertension with ACE inhibitors, which can result in decreased production of Ang II and increased expression of ACE2, effectively decreases the production of inflammatory cytokines. ACE inhibitors that are able to reduce the production of inflammatory cytokines are potential drug candidates for the treatment of COVID-19 patients and pre-existing hypertension (Yang et al., 2020). Treatment with ACE inhibitors in patients with hypertension has a therapeutic effect in lowering blood pressure, so it is important to determine the outcome with their use in COVID-19 patients, which is also associated with lower mortality, but the potential benefit of ACE inhibitors in COVID-19 cases remains uncertain. Thus, we carried out a systematic review and meta-analysis aimed at finding out how much influence

ACE inhibitors in COVID-19 patients with hypertension have on mortality rates.

SUBJECTS AND METHOD

1. Study Design

Systematic Review and Meta-Analysis are the methods chosen in this study. The articles selected and used in this study are articles published from 2020 to 2021. We conducted a comprehensive literature search from March 4 to March 15, 2022 from three types of databases including PubMed, Google Scholar, and Science Direct. The search used a specific keyword strategy as follows: "ACE inhibitor" AND "COVID-19" AND "Hypertension" AND "mortality". After screening by identifying relevant abstracts, we searched the reference list from retrieved articles to find additional potentially compliant study requirements.

2. Inclusion Criteria

Full-text article using a cohort study design. The research subjects were confirmed COVID-19 patients. The study outcome was mortality. Multivariate analysis with adjusted odds ratio (aOR) to measure the estimated effect.

3. Exclusion Criteria

Articles published in languages other than English. Statistical results are reported in the form of bivariate analysis. Articles before 2020.

4. Operational Definition of Variables

The article search process considers the eligibility criteria determined by the PICO model. Q: COVID-19 patient with hypertension. I: Administration of ACE inhibitor therapy C: Treatment other than ACE inhibitors and O: Mortality.

ACE inhibitors or Angiotensin-converting enzyme (ACE) inhibitors as pharmacotherapy that can be useful for the treatment of hypertension, heart failure and chronic kidney failure. ACE inhibitors can relax the walls of blood vessels so they can lower blood pressure. The instruments used are medical records and officer records regarding the chronic diagnosis of COVID-19 disease with hypertension. The measurement scale is categorical.

Hypertension is a condition where systolic blood pressure is more than 140 mmHg and diastolic is more than 90 mmHg. Hypertension as a dangerous non-communicable disease (PTM).

COVID-19 is a disease caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Disorders of the respiratory system, ranging from mild clinical conditions such as flu, to lung infections, such as pneumonia as a condition caused by COVID-19

COVID-19 patient mortality is a mortality status of patients diagnosed with COVID-19 who have hypertension. The tool used is a mortality certificate document with a diagnosis of COVID 19. The measurement scale is categorical.

5. Study Instruments

This research study is guided by the PRISMA diagram and article quality assessment using the Critical Appraisal Skills Program (CASP, 2018).

6. Data Analysis

The Review Manager application (RevMan 5.4) was used to analyze the data in this study. Forest plots and funnel plots were used to measure the relationship and heterogeneity of the data.

RESULTS

This meta-analysis begins with journal identification, which is looking for articles from several guide journals containing databases including Pubmed, Google Scholar and Science Direct with the specified key word. Next is the review process of the article through the use of the PRISMA diagram (Figure 1).

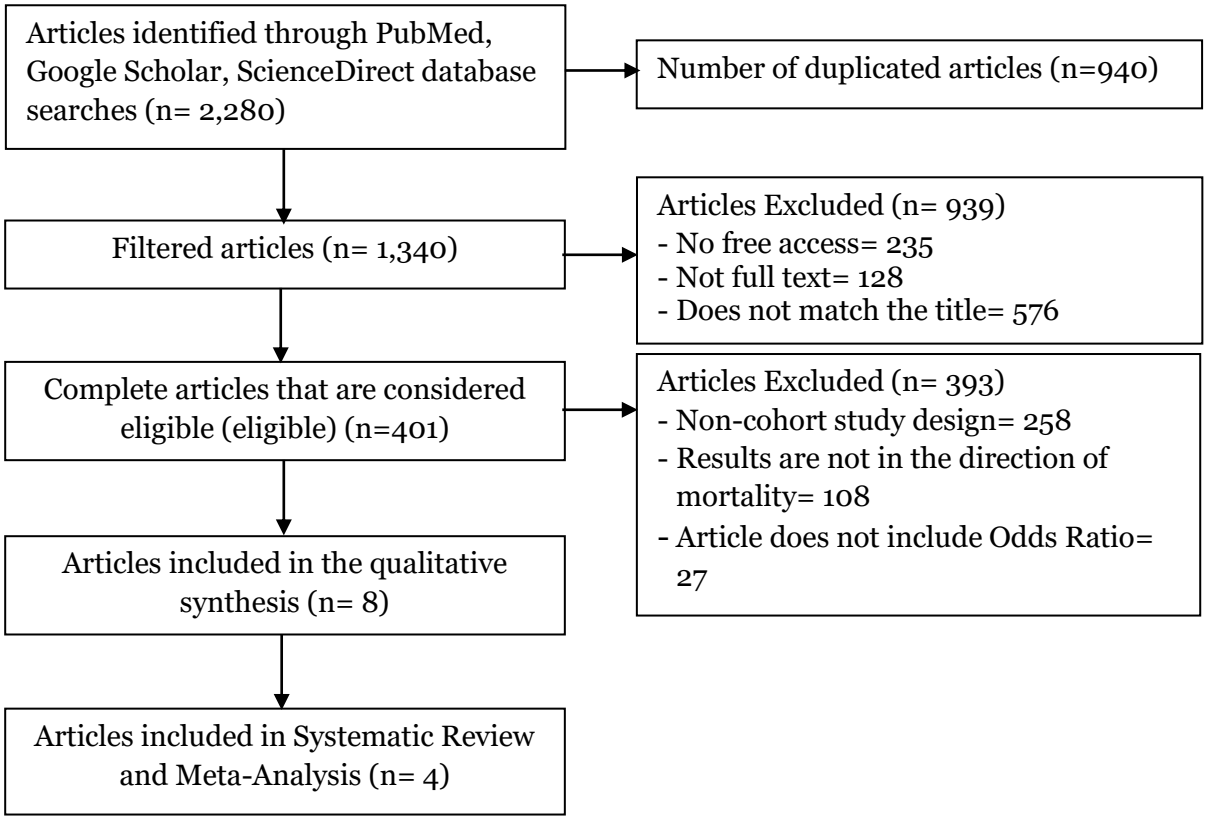

Figure 1. PRISMA Flowchart

Figure 2. Map of study area Effect of ACE inhibitor therapy on COVID-19 Patients with Hypertension Against Mortality

Research related to mortality of COVID-19 patients who were hospitalized and had hypertension co-occurring by receiving ACE inhibitor therapy was 817 articles, from the initial search process as many as 2,280 articles. The next step is to exclude the same articles (removing duplicate articles) followed by a screening process so that 18 articles that meet the requirements for further review work are obtained. And as many as 4 articles that meet and are in accordance with the quality assessment to be used in quantitative synthesis using meta-analysis.

It can be seen in Figure 2. that the research articles come from 3 countries, namely America, China and Italy.

In Table 1, the researcher conducted an assessment of the quality of the study using the Critical Appraisal Skills Program (CASP). Meanwhile, Table 2 describes the description of the main studies included in the primary learning meta-analysis which shows that 4 articles from observational studies (cohorts) provide evidence that the administration of ACE inhibitor therapy in patients diagnosed with COVID-19 with concomitant high blood pressure or hypertension who are hospitalized hospitalization affects the patient's mortality rate.

Table 1. Assessment of study quality published by the Critical Appraisal Skills Program (CASP)

No	Indicators	Publication (Author and Year)			
		Yan et al. (2020)	Polverino et al. (2020)	Lam et al. (2020)	Bauer et al. (2020)
1	Did the study address a clearly focused issue?	2	2	2	2
2	Was the cohort recruited in an acceptable way?	2	2	2	2
3	Was the exposure accurately measured to minimise bias?	2	2	2	2
4	Was the outcome accurately measured to minimise bias?	2	2	2	2
5	Have the authors identified all important confounding factors? Have they taken account of the confounding factors in the design and/or analysis?	2	2	2	2
6	Was the follow up of subjects complete enough? Was the follow up of subjects long enough?	2	2	2	2
7	What are the results of this study?	2	2	2	2
8	How precise are the results?	2	2	2	2
9	Do you believe the results?	2	2	2	2
10	Can the results be applied to the local population?	1	1	1	1
11	Do the results of this study fit with other available evidence?	2	2	2	2
12	What are the implications of this study for practice?	1	2	2	2
	Total	**22**	**23**	**23**	**23**

Note: 2: Yes; 1: Can't tell; 0: No

Table 2. Description of the Primary Study

No	Author, Year	Study Design	Country	Sample		Population	Intervention	Comparison	Outcome	aOR (95%CI)
				Total	ACE Inhibitor Therapy					
1	Yan et al. (2020)	Retrospective Cohort	China	2,190	655	COVID-19 patients with hypertension	ACEi, ARB, CCB, BB and Thiazide therapy	Without ACEi, ARB, CCB, BB and Thiazide Therapy	Disease severity and mortality	0.49 (0.18 to 1.34)
2	Polverino et al. (2020)	Cohort	Italia	5,625	3.179	COVID-19 patient with hypertension and cardiomyo-pathy aged 65 years	ACEi, ARB, BB or Ca antagonist therapy	No ACEi, ARB, BB or Ca . antagonist therapy	Mortality	0.97 (0.73 to 1.29)
3	Lam et al. (2020)	Retrospective Cohort	USA	6,235	614	COVID-19 patients with hypertension	ACEi and ARB Terapi therapy	ACEi and ARB Terapi therapy	Mortality	0.215 (0.10 to 0.45)
4	Bauer et al. (2020)	Cohort	AS	1,449	550	COVID-19 patients with hypertension	ACEi and ARB Terapi therapy	ACEi and ARB Terapi therapy	Disease severity and mortality	1.30 (0.93 to 1.181)

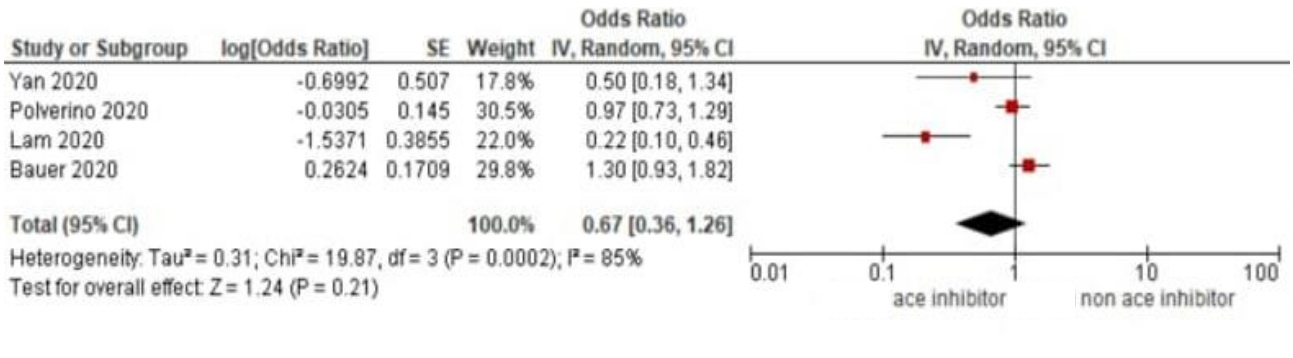

Figure 3. Forest plot effect of ace inhibitor therapy on mortality in COVID-19 patients with hypertension

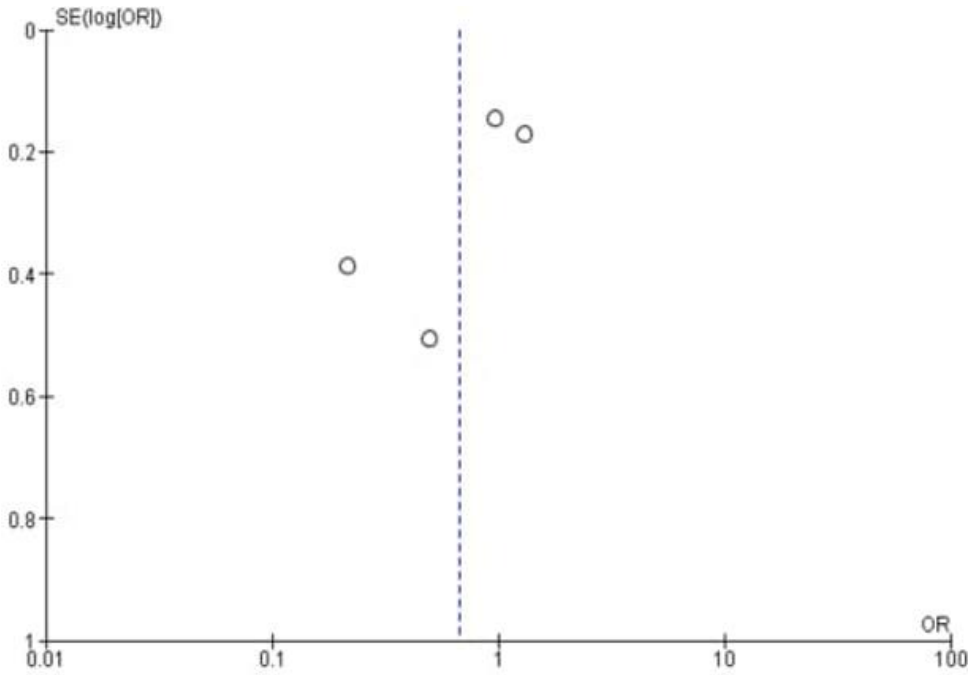

Figure 4. Funnel plot effect of ace inhibitor therapy on mortality in COVID-19 patients with hypertension

Based on the results of the forest plot, an observational study (cohort) showed that the mortality rate of COVID-19 patients with comorbid hypertension who were given ACE inhibitors reduced the risk of mortality 0.67 times compared to COVID-19 patients with hypertension who were not given ACE inhibitor therapy (OR= 0.67; 95% CI= 0.36 to 1.26), and the results were not statistically significant (p=0.210). With the heterogeneity of the research data, I^2= 85% so that the distribution of the data is said to be heterogeneous (random effect model).

The funnel plot results in publication bias with an overestimated effect which is indicated by the asymmetry of the distribution between the right and left plots. There are two plots on the right and two plots on the left. The plot on the right side of the graph has a standard error (SE) between 0 and 0.2. The plot on the left side of the graph has a standard error (SE) between 0 and 0.5.

DISCUSSION

It is known that comorbid conditions play a relevant role in increasing the mortality risk of patients with COVID-19, in particular, hypertension and cardiovascular underlying and associated mortality in hospitalized COVID-19. The case fatality rate tends to be high in the elderly and individuals with co-existing hypertension (Polverino et al., 2020). This study discusses ACE inhibitor therapy in hypertension which is considered important because it is one of the risk factors that reduce mortality in COVID-19 patients. In line with Polverino et al. (2020) that COVID-19 patients who were hospitalized and had comorbid hypertension there was no increased risk of death associated with the use of ACE inhibitors (OR= 0.97; 95% CI= 0.73 to 1.29). Another finding by Lam et al. (2020) which is to analyze the use of ACE inhibitors or ARBs in hospitals received by COVID-19 patients with hypertension and other confounding variables that may result in discontinuation of ACE inhibitor therapy or the use of ARBs. The main finding was that hypertensive patients with COVID 19 who continued ACE inhibitors or ARBs in the hospital had less mortality in the hospital and less frequent ICU admissions when compared to patients who discontinued their ACE inhibitors or ARBs in the hospital (OR=0.215; 95%CI= 0.101 to 0.455).

Several studies stated that disease severity using ACE inhibitors was statistically significantly reduced in elderly patients (OR= 0.16; 95% CI= 0.04 to 0.67; p= 0.013) (Yan F et al., 2020). Furthermore, in the same study, Yan F et al (2020) stated that hypertensive patients should continue to take ARBs and ACEIs during the COVID-19 pandemic. The study shows that antihypertensive drugs ARB, ACEI, CCB, and BB may have the potential to be an economical and effective drug for COVID-19 patients, especially elderly patients. According to a study conducted by Bauer (2020) that cardiovascular comorbidities are associated with severe COVID-19, especially among patients under the age of 65. The investigators did not find a substantially increased risk of severe COVID-19 among patients taking antihypertensives with severe coronavirus disease 19 (COVID-19) as in hospitalization. (OR= 1.30; 95% CI= 0.93 to 1.81)

Hypertension is a common comorbidity that can occur in patients with coronavirus disease 2019 (COVID-19) and has been adjusted for worse clinical outcomes. Widely used antihypertensive drugs such as ACE inhibitors and ARBs can upregulate ACE2 receptors (Lam et al., 2020).

Patients with COVID-19 who continue therapy with ACE inhibitors or ARBs during hospitalization may experience a reduced side effect of hypertension, which is a well-known risk factor for death in COVID-19. ACE inhibitors or ARBs have a cardioprotective effect in patients with post-myocardial infarction and heart failure by reducing myocardial wall stress. In addition, ACE inhibitors or ARBs have been shown to reduce microvascular complications in patients with cardiac, cerebrovascular, and renal comorbidities. Experimentally, ACE inhibitors and ARBs have the ability to upregulate ACE2, leading to the degradation of angiotensin II and increased formation of angiotensin which is thought to be beneficial for its vasodilating, anti-inflammatory, and antifibrotic effects. It is also interesting that ACE inhibitors or ARBs play a role in ameliorating the detrimental effects of the cytokine storm seen during the immune response to SARS-CoV-2, a condition that has been associated with the proinflammatory effect of angiotensin

II, suggesting a primary pulmonary protective role (Lam et al., 2020).

Several modifiable risk factors are potentially associated with increased susceptibility to infection or poorer outcomes among those with comorbid cardiovascular disease, hypertension, and diabetes. The use of ACE inhibitor or ARB therapy may influence the ability of SARS-CoV- 2 to infect cells via upregulation of angiotensin-converting enzyme 2 (ACE2), the receptor for SARS-CoV cell entry (Fosbøl et al., 2020).

SARS-CoV-2 is characterized by a spike protein that allows the binding of the virus to the angiotensin-converting enzyme (ACE)-2, which acts as a viral receptor and is expressed on the surface of several types of pulmonary and extrapulmonary cells, including cardiac, kidney, gut, and endothelial cells. There is evidence that endothelial cells are also infected by SARS-CoV-2, with systemic vasculitis, thromboembolism, and disseminated intravascular coagulation occurring. These effects, together with a "cytokine storm" are implycated in a poorer prognosis. In clinical practice, angiotensin converting enzyme inhibitors (ACE-inhibitors) and angiotensin II receptor blockers (ARBs) are widely used for the treatment of hypertension and other cardiovascular diseases. In in vivo studies, ACE inhibitors and ARBs appear to paradoxically increase ACE-2 expression, which may favor SARS-CoV-2 infection in host cells and tissues. In contrast, in patients treated with ACE inhibitors and ARBs, ACE-2 showed downregulation of mRNA and protein levels in kidney and cardiac tissue. And it has been claimed that ARBs and ACE inhibitors are potentially useful in the clinical care of patients infected with SARS-CoV-2. (Albini et al., 2020).

The most dominant comorbidities in patients dying from COVID-19 were hypertension, diabetes, and cardiovascular disease. Older patients with COVID-19 with cardiovascular comorbidities have a poorer clinical course and poorer prognosis, with many of them also being treated with ARBs or ACE inhibitors. Viral entry also depends on the activity of the protease TMPRSS2, an androgen-dependent enzyme. Regardless of the relevance of animal studies, to comprehensively address the question of the potential harm or benefit of ACE inhibitors and ARBs in the clinical course of patients affected by COVID-19 treated with these anti-hypertensive drugs, further research is necessary. A sufficiently robust prospective study aimed at answering important questions for cardiovascular, internal and emergency medicine (Albini et al., 2020).

In a meta-analysis taken from four articles by Yan et al. (2020); Polverino et al. (2020); Lam et al. (2020); and Bauer. (2021) most of the studies evaluated have shown that the use of ACE inhibitors in the treatment regimen of COVID-19 patients with hypertension is beneficial.

These studies show that the continued use of ACE inhibitors or ARBs in COVID-19 hypertensive patients results in better clinical outcomes (Lam et al., 2020). The limitations of this study are that there is a language bias because it only uses English articles and a search bias because it only uses three databases.

AUTHOR CONTRIBUTION

Dwi Trisnawati Zainal as the main researcher, designed this research, collected articles from electronic journal databases and analyzed the data.

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CONFLICT OF INTEREST

There is no conflict of interest in this study.

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