AN UPDATED META-ANALYSIS: THE EFFECT OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS IN THE MORTALITY OF HYPERTENSIVE PATIENTS WITH CONFIRMED COVID-19 INFECTION

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ABSTRACT

Background: At present, there are over 26 million cases of confirmed COVID-19 infection worldwide. Locally, the Philippines had recorded a total of 232,072 cases with 3,737 patients who succumbed to the disease. One of the most common co-morbidities identified among these patients was hypertension. Debates on use of Angiotensin-Converting Enzyme Inhibitors (ACEI) and Angiotensin-Receptor blockers (ARB) emerged due to an interaction of the said drugs with Angiotensin-converting enzyme 2 (ACE2), an enzyme which is a point of entry of coronavirus. This study aims to give an update on the work of Zhang *et al*[13] in exploring the association of ACEI/ARB use on mortality and disease severity.

Methods: This meta-analysis involves review of observational studies among hypertensive patients with composite data on ACEI and ARB use. Analyses were performed determining the odds ratio of each event using the raw data obtained from each study. Random effects model and Cochran-Mantel-Haenszel Method were utilized at 95% confidence interval. To check for heterogeneity, X^2 test and I_2 statistic were calculated. Subgroup analyses on ACEI users and ARB users were also done. Cochrane Review Manager (REVMAN 5.3) was used and Forest plots were generated. In this update, the total population of patients with confirmed COVID-19 infection was more than 50,000 with hypertensive patients comprising more than half of the sample population. The analyses done manifested decreased frequency of both outcomes with ACEI/ARB use.

Results: The calculated odds ratio for mortality and disease severity were 0.63 and 0.56, respectively. However, a statistically significant heterogeneity existed for both outcomes. Subgroup analyses among ACEI users versus ACEI/ARB non-users (odds ratio for mortality = 0.95, I^2 = 0%; and odds ratio for disease severity = 0.30, I^2 = 0%), and ARB users versus ACEI/ARB non-users (odds ratio for mortality = 0.70, I^2 =f 68%; and odds ratio for disease

severity = 0.48, I^2 = 77%) also manifested decreased frequency of both outcomes. However, significant heterogeneity exists among the ARB users, which is in contrary among the ACEI users. **Conclusion:** The use of ACEI contributes to a statistically significant reduction of mortality and disease severity among hypertensive patients with confirmed COVID-19 infection. We recommend continuing analysis of association of ACEI and ARB use and clinical outcomes since recent analysis suggests a beneficial effect especially in the ACEI group. At present, our findings are still in line with the current recommendation to not discontinue the use of ACEI and ARB among our hypertensive patients.

Keywords: *COVID-19 infection, Angiotensin-converting enzyme inhibitor, Angiotensin receptor blocker, hypertension, mortality rate, disease severity*

BACKGROUND OF THE STUDY

At present, the world faces a pandemic – the occurrence of a novel strain of coronavirus (SARS-CoV-2) from Wuhan, China which causes the COVID-19 infection. There are over 26 million cases of confirmed COVID-19 infection worldwide with more than 800,000 people who succumbed to the said infection based on the World Health Organization. Locally, the Philippines had recorded a total of 232,072 cases with 3,737 patients who died based on the census of the Department of Health. Since November 2019, studies about this disease, including its pathophysiology and management, flooded the medical and scientific industries. The searches for a definite treatment and effective vaccination are still on phases of human trial. Hence, baseline characteristics and demographic profiles of patients with confirmed COVID-19 infection were identified to determine risk factors for having this disease.

In a study by Guan *et al*[1], out of 1099 patients with laboratory-confirmed COVID-19 infection, the prevalence of hypertension is 15%, with diabetes, chronic obstructive pulmonary disease and chronic kidney disease at 7.1%, 1.4% and 0.7%, respectively. Meanwhile, according to Schiffrin *et al*[2], there are co-morbidities which were noted to increased the risk for COVID-19 infection and worse outcomes due to increased severity of lung injury. The most common co-morbidity in one report was hypertension at 30%, followed by diabetes and coronary artery disease at 19% and 8%, respectively. Thus, adequate blood pressure control is emphasized.[2]

However, debates on the continuation of use of RAAS inhibitors, particularly, Angiotensin-Converting Enzyme Inhibitors (ACEI) and Angiotensin-Receptor blockers (ARB) emerged. This was due to an interaction of the said drug classes with the Angiotensin-converting enzyme 2 (ACE2), an enzyme which is noted to also be a functional receptor and a point of entry of coronavirus.

In 2003, after the outbreak of severe acute respiratory syndrome (SARS) in 2002 due to SARS-CoV, Kuba *et al* first identified ACE2 as a functional SARS coronavirus receptor in cell lines.[3] ACE2 is expressed in the heart, testis, kidneys and lungs in high amounts.[9] *In vivo* experiments on wild-type mice showed that reduced ACE2 expression might have a role in severe acute lung pathologies of SARS.[3] SARS-CoV-2 has 80% similarity in sequence identity with SARS-CoV.[10] Having the same viral genotype, SARS-CoV-2 is able to enter the human cell through ACE2 receptors. ACE2 is said to counterbalance the effect of ACE, thus, while ACE is responsible to convert Angiotensin I to Angiotensin II, ACE2 acts to generate Angiotensin I from Angiotensin II leading to a vasodilatory effect with an unclear contribution to the pathogenesis of COVID-19 infection.[4]

Ingrahan *et al*[10] in 2020 coined the term Renin-Angiotensin-Aldosterone-SARS-CoV-Axis. In their review, Angiotensin II has two receptors namely type 1 Angiotensin II (AT_1) and type II Angiotensin II (AT_2). AT_1 plays a role in inflammation, vasoconstriction and atherogenesis, while AT_2 is associated with vasodilation, decreased platelet aggregation and upregulation of insulin action. AT_2 is noted to be in low amounts among healthy individuals. Thus, Angiotensin II is counterbalanced by ACE2 which has equal effects as seen from AT_2 stimulation. An excess of Angiotensin II leads to increased membrane permeability and increased epithelial cell apoptosis, promoting inflammation, pulmonary vasoconstriction and cytokine-induced organ damage. It is said that overstimulation of the AT_1 receptor in the lungs causes acute lung injury and acute respiratory distress syndrome which may lead into death. ACEI decreases Angiotensin II levels due to inhibition of conversion of Angiotensin I to Angiotensin II, however at clinical doses, it is said that ACEI can affect as much of this conversion because 40% of the transformation of

Angiotensin II happens outside the ACE pathway. On the other hand, Angiotensin II level is noted to be increased in response to ARB except in the kidneys.

Studies regarding the association of using ACEI and/or ARB and ACE2 expressions were variable.[2] Some studies claim that the use of ACEI and ARB causes upregulation of ACE2 while others suggest downregulation of the said enzyme.[3] There are also some studies indicating no association of the said antihypertensive medications to ACE2 expression.[4] In a study by Sama *et al*[9] in March 2020, plasma concentrations of ACE2 were compared among male and female patients with heart failure, and it was found out that said concentrations were higher in male patients however, the use of ACEI and/or ARB was not associated with higher plasma ACE2 concentrations.

Hence, physicians now face additional challenge among patients with confirmed COVID-19 infection who are using ACEI and/or ARB as antihypertensive medication. Currently, there is still no randomized controlled trial depicting direct association of ACEI and ARB on COVID-19 infection.

Five meta-analyses[13, 14, 27, 28] tackling the possible association of using RAAS inhibitors among hypertensive patients with confirmed COVID-19 infection, and mortality and/or disease severity were identified. Liu *et al*'s work in March 2020[27] found that there was no statistical significance between using any of the five types of anti-hypertensive medications, namely, ARB, ACEI, Calcium-Channel blockers, Thiazides and Beta-blockers, and disease severity. The studies of Zhang *et al*[13], Pirola and Sookoian[14],and Usman *et al*[28] also concluded that there was no association between use of ACEI/ARB and risk of severity of COVID-19 infection and/or death. On the contrary, a study by Baral *et al*[29] stated a decreased risk of death or critical events with RAAS inhibition. Furthermore, Usman *et al*[28] and Zhang *et al*[13] suggested that neither ACEI nor

ARB use had a statistically significant association with the odds of testing positive with COVID-19 infection. Interestingly, Liu *et al*[27] also mentioned that among elderly patients aged > 65y/o, use of ARB is associated with decreased risk of having severe COVID-19 infection, while Pirola and Sookoian[14] stated that the use of ACEI contributed to ~35% reduction in the risk of death or critical disease which may explain the overall protection manifested by RAAS inhibitors in their obtained data.

Indeed, majority of the studies showed no association between use of ACEI and ARB with mortality and disease severity of hypertensive patients with confirmed COVID-19 infection. However, it was noteworthy to mention that except for the study of Zhang *et al*[13], the other meta-analyses did not use a composite data on users of ACEI and ARB consistently. Redundancy among involved subjects may have occurred due to the possibility that a single patient may have been using both ACEI and ARB for blood pressure control. Furthermore, some of the meta-analyses included data for other types of RAAS inhibitors aside from ACEI and ARB, such as aldosterone antagonists and renin inhibitors, which are not present in majority of the studies.

Hence, this study aims to update the work of Zhang *et al*[13] which utilized nine studies for association of ACEI and ARB use and mortality, and seven studies for association of ACEI and ARB use and disease severity among hypertensive patients with confirmed COVID-19 infection. This meta-analysis included total of 17 studies in the analyses. However, in order to avoid redundancy in the data, this study used composite data of over-all mortality rate of COVID-19 confirmed patients who used ACEI and ARB. Also, this study is limited only to published articles in the English language. No analysis for safety profile was done in this study since majority of the utilized studies did not have data on this aspect. Probably, this is because ACEI and ARB are both

recommended for the treatment of hypertension based on the existing guidelines for hypertension with compelling established indications and contraindications indicated as well.

RESEARCH QUESTION

Among hypertensive patients with confirmed COVID-19 infection, does the use of Angiotensin-Converting Enzyme Inhibitors (ACEI) and Angiotensin Receptor Blockers (ARB) increase the over-all mortality rate from dying from COVID-19 infection?

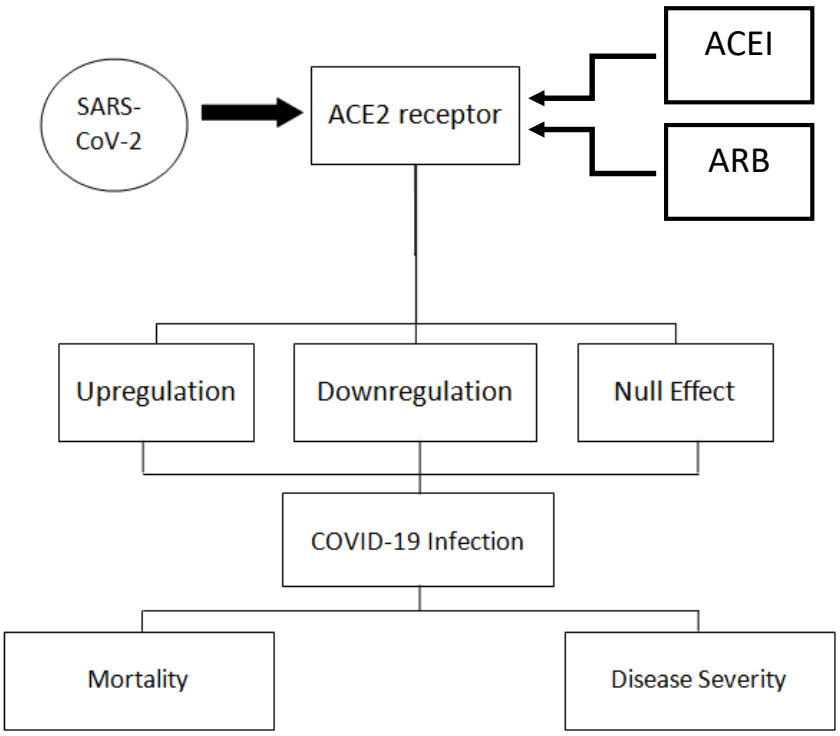

Figure 1. Conceptual Framework: Expression of ACE 2 receptor, a known receptor for SARS-CoV-2 may be affected by use of RAAS inhibitors, which may contribute to mortality and/or disease severity of hypertensive patients with confirmed COVID-19 infection. *ACE2 receptor, Angiotensin-Converting Enzyme 2; ACEI, Angiotensin-Converting Enzyme Inhibitor; ARB, Angiotensin Receptor Blocker*.

SIGNIFICANCE OF THE STUDY

This meta-analysis aims to give an update on the association between the use of ACEI and ARB, among hypertensive patients with confirmed COVID-19 infection, and mortality rate. Furthermore, its association with disease severity was also explored. This study aims to strengthen the recommendation whether physicians can advise continuation of ACEI and/or ARB use for control of hypertension among their patients with confirmed COVID-19 infection, or opt for another anti-hypertensive medication for optimal blood pressure control.

OBJECTIVES

The general objective of this meta-analysis is to compare the over-all mortality rate of hypertensive patients with confirmed COVID-19 infection who are ACEI/ARB users from non-ACEI/ARB users. Furthermore, this study also aims to elucidate if an association between use of ACEI and/or ARB, and disease severity exists to the said sample population.

METHODOLOGY

I. Search Strategy

Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines was used. An update of the previous study by Zhang *et al*[13] was done. The literature search included studies published from December 2019 until June 30, 2020. Studies used in the mentioned meta-analyses which had data on composite ACEI and ARB users upon re-evaluation were also included, however, we were not able to re-examine one study due to no English translation available, and two studies due to lacking of details on the list of references. Manual searching of the missing articles were also tried to no avail. Furthermore, keywords “RAAS inhibitors”, “ACE

inhibitor", "ARB", "ACE2", "COVID", "mortality", "disease severity" and "critical" were utilized in different word combinations to obtain published journals and articles from the PubMed, Google Scholar and UpToDate databases. Hand search was also used.

II. Study Design

This meta-analysis involves review of observational studies among hypertensive patients with confirmed COVID-19 infection which detail the use of ACEI and ARB, with primary outcome of mortality. Secondary outcome for disease severity or critical COVID-19 infection was also determined. Presence of bias in the obtained data was assessed by heterogeneity analysis and generation of Funnel plots.

III. Ethical Considerations

The protocol of this study adhered to the ethical considerations and principles in relevant guidelines, including harmonization – Good Clinical Practice, Data Privacy Act of 2012 and National Ethics Guidelines for Health Research. Data were obtained from retrospective observational studies.

IV. Data Collection

The studies reviewed and evaluated in this meta-analysis were those with the following criteria: 1) observational and/or retrospective studies; 2) hospitalized adult patients (18y/o and above) diagnosed with COVID-19 infection; 3) with a data of usage of ACEI and/or ARB as maintenance medication for hypertension; and 4) with disclosed information on clinical outcome as to severity of illness, mortality and/or survival. There were total of 17 journals which were

evaluated for the final assessment. In the primary analysis, a total of 12 studies were included in the data treatment, because upon review, four studies[5, 18, 22, 31] had no composite data on ACEI and ARB users, while one study[23] failed to cite the total hypertensive patients with COVID-19 infection. In these 12 studies, only 10 researches were used for the primary outcome, and eight researches were utilized for the secondary outcome, because not all study explored on both outcomes. Furthermore, in the subgroup analyses, three studies were used in the ACEI group, and four studies were evaluated in the ARB group. The included studies were limited to those using the English language.

V. Exclusion Criteria

The studies which were excluded in this meta-analysis were: 1) articles in reaction to a journal (i.e. letter, editorial, opinion, commentary); 2) proposed prospective trial; 3) reviews of published papers; 4) abstract; 5) case report; 6) study utilizing databases from multiple countries; 7) research with inadequate report on combined use of ACEI and ARB; and 8) research with inadequate report on mortality and/or disease severity of patients in the study population. Three articles used previously in the aforementioned meta-analyses cannot be retrieved due to lacking of search details. One of these articles is in Chinese language and has no available English translation during the time of search.

VI. Measurement of Outcomes

The primary outcome used in this study was mortality among hypertensive patients with confirmed COVID-19 infection maintained on ACEi and/or ARB for adequate blood pressure control. The secondary outcome was disease severity on the said sample population.

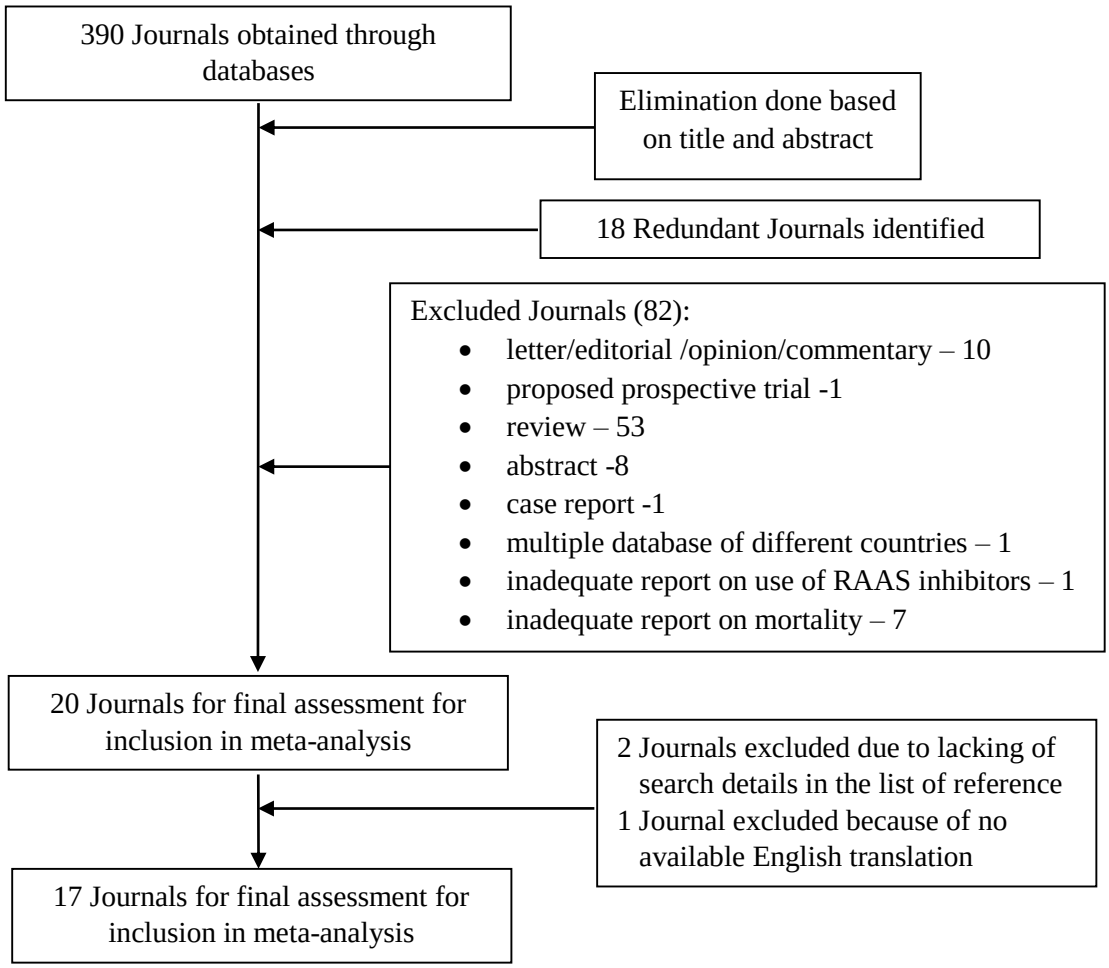

Figure 2. PRISMA Flowchart.

Table 1. List of articles reviewed including previous meta-analyses published.

Article	**Date Published**	**Duration of Study**	**Total Number of Patients with COVID-19 Infection**	**Total Number of Hypertensive Patients with COVID-19 Infection**	**ACEI/ARB Users**	**ACEI/ARB Non-Users**	**Outcome/s**
Bean, D.M. *et al*	May 2020	Mar 1 – Apr 13, 2020	1200	645	339	306	Death Admission to critical care unit for organ support within 21 days of symptoms onset

Conversano, A. *et al*	May 2020	Feb 27 – Mar 17, 2020	212	96	69	27	Mortality
Feng, Y. *et al*	April 2020	Jan 1 – Feb 15, 2020	476	113	33	80	Systemic Organ Index
Fosbøl, E. *et al*	June 2020	Feb 1 – May 4, 2020	4480	843	634	209	All-cause death, severe COVID-19 or ICU admission
Guo, T. *et al*	March 2020	Jan 23 – Feb 23, 2020	187	61	19	42	Death with or without elevated Troponin T levels
Huang, Z. *et al*	March 2020	Feb 7 – Mar 3, 2020	----	50	20	30	Clinical severity, clinical course, short-term outcome
Ip, A. *et al*	April 2020	----	3017	1584	460	1124	Discharge, Death
Khera, R. *et al*	May 2020	Jan 5 – May 10, 2020	12,566	7933	4587	3346	In-patient hospitalization, mortality during hospitalization
Li, J. *et al*	April 2020	Jan 15 – Mar 15, 2020	1178	362	115	247	Mortality, severity
Li, X. *et al*	April 2020	Jan 26 – Feb 5, 2020	548	166	42	124	Association between age, sex, source of infection and underlying co-morbidity
[a]Liu, Y. *et al*	March 2020	Jan 11 – Feb 5, 2020	511	----	----	----	Disease severity in elderly COVID-19 patients

[b]Mancia, G. *et al*	June 2020	Feb 21 – Mar 11, 2020	6272	3632	----	----	Risk Severity
[b]Mehra, M. *et al*	May 2020	Dec 20, 2019 – Mar 15, 2020	8910	2346	----	----	In-hospital death
Mehta, N. *et al*	May 2020	Mar 8 – Apr 12, 2020	1735	----	211	----	Positive COVID-19 result, clinical outcomes
Meng, J. *et al*	March 2020	Jan 11 to Feb 23, 2020	417	51	17	34	Disease Severity Mortality, Level of IL-6
[a]Pirola, C. & Sookoian, S.	May 2020	Dec 2019 – May 9	24,676	----	----	----	Effect on COVID-19 outcome
Reynolds, H.R. *et al*	June 2020	Mar 1 – Apr 15, 2020	5894	4357	2141	2216	ICU admission, Use of mechanical ventilation, Death
Richardson, S. *et al*	April 2020	Mar 1 – Apr 4, 2020	5700	3026	----	----	Invasive mechanical ventilation, ICU care, Absolute Lymphocyte Count, Acute Kidney Injury, Kidney Replacement Therapy, Acute Hepatic Injury, Death
Tedeschi, S. *et al*	April 2020	Feb 22 – Apr 4, 2020	609	311	----	----	Mortality

[a]Usman, M. *et al*	May 2020	May 2020	62,706	20,316	----	----	Risk of testing positive, mortality
Yang, G. *et al*	April 2020	Jan 5 – Feb 22, 2020	462	126	43	83	Disease status
Zeng, Z. *et al*	April 2020	Jan 5 – Mar 8, 2020	274	75	28	47	28-day Mortality, Severity of Pneumonia, Length of Hospital Stay, Discharge Rate, Hospitalization Rate
Zhang, P *et al*	May 2020	Dec 31, 2019 to Feb 20, 2020	3611	1128	188	940	All-cause mortality
[a]Zhang, X. *et al*	May 2020	Jan 1 – May 9, 2020	19,000	----	----	----	Mortality, Disease Severity

[a]Meta-analysis
[b]Data was collected from multiple registries from different states/countries.

VII. Statistical Analysis

Analyses were performed for both primary and secondary outcomes by determining the odds ratio of each event using the raw data obtained from each article (See Appendix). Random effects model and Cochran-Mantel-Haenszel Method were used to know if an association exist between ACEI/ARB use and mortality, and ACEI/ARB use and disease severity. A 95% confidence interval was utilized. To check for heterogeneity of samples, X^2 test and I_2 statistic were calculated. An I^2 of more than 50% or a P value < 0.05 for the Q statistic pertains to significant heterogeneity among the sample populations used. Funnel plots were extrapolated to check for

publication bias due to variable sample sizes. A P value < 0.05 was considered statistically significant. Subgroup analyses using articles with separate data on ACEI users and ARB users were also done. Cochrane Review Manager (REVMAN 5.3) was used in this analysis, and Forest plots were generated.

RESULTS

In this update, the total population of patients with confirmed COVID-19 infection was more than 50,000 with hypertensive patients comprising more than half of the sample population (more than 26,000). The Forest plots generated for both outcomes – mortality and disease severity (Fig. 3 and Fig.4), portrayed inverse associations of use of ACEI and ARB with mortality and disease severity of COVID-19 infection among hypertensive patients in the adult population. At 95% confidence interval, the odds ratios for mortality and disease severity were 0.63 (0.40, 0.99), and 0.56 (0.24, 1.29), respectively. The test of overall estimate effect for both outcomes had P < 0.04 for mortality and P = 0.18 for disease severity. Heterogeneity of sample populations in both outcomes was evaluated. Calculated I^2 values for mortality and disease severity were 87% (P < 0.00001) and 89% (P < 0.00001), respectively. Funnel plots (Fig. 5) were also generated to see for publication bias.

Subgroup analyses among ACEI and ARB users reaching the primary and secondary outcomes were also done (Figures 6 and 7). Among ACEI users versus ACEI/ARB non-users, the calculated odds ratio for outcome of mortality was 0.95 (0.82, 1.11), with an I^2 of 0% (P = 0.48) (Fig. 6a), while the calculated odds ratio of outcome of disease severity was 0.30 (0.10, 0.94), with an I^2 of 0% (P = 0.55) (Fig. 6b), both at 95% confidence interval. On the other hand, among ARB users versus ACEI/ARB non-users, the computed odds ratio for outcome of mortality was 0.70

(0.31, 1.59), with an I^2 of 68% (P = 0.04) (Fig. 7a), while the computed odds ratio for outcome of disease severity was 0.48 (0.11, 2.08), with an I^2 of 77% (P = 0.04) (Fig. 7b), both at 95% confidence interval as well.

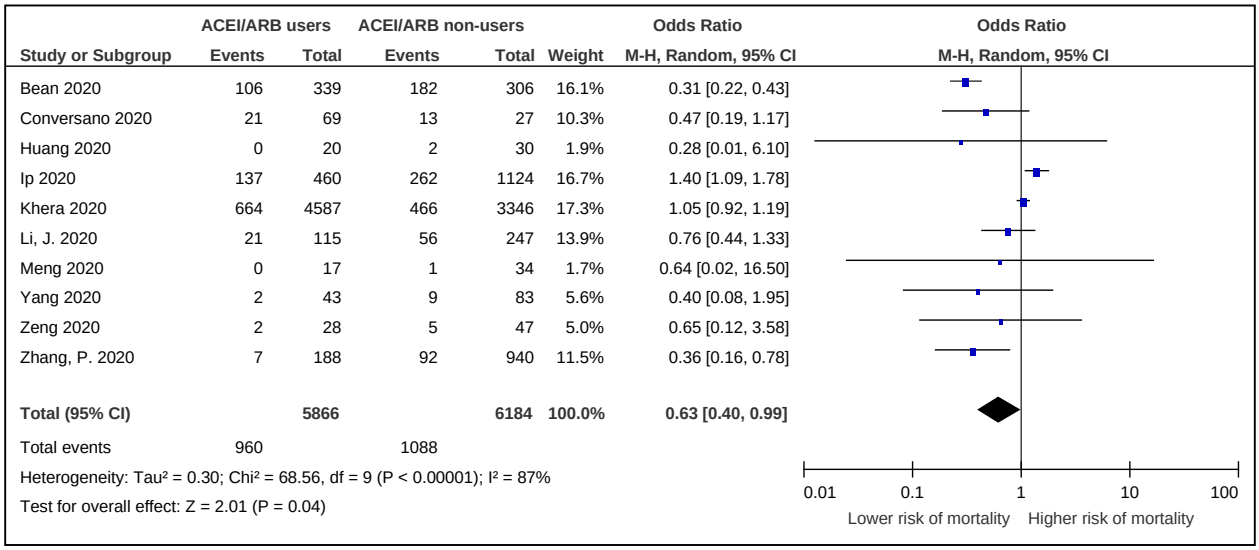

Figure 3. Forest plot for association of ACEI/ARB use with mortality among hypertensive patients with confirmed COVID-19 infection.

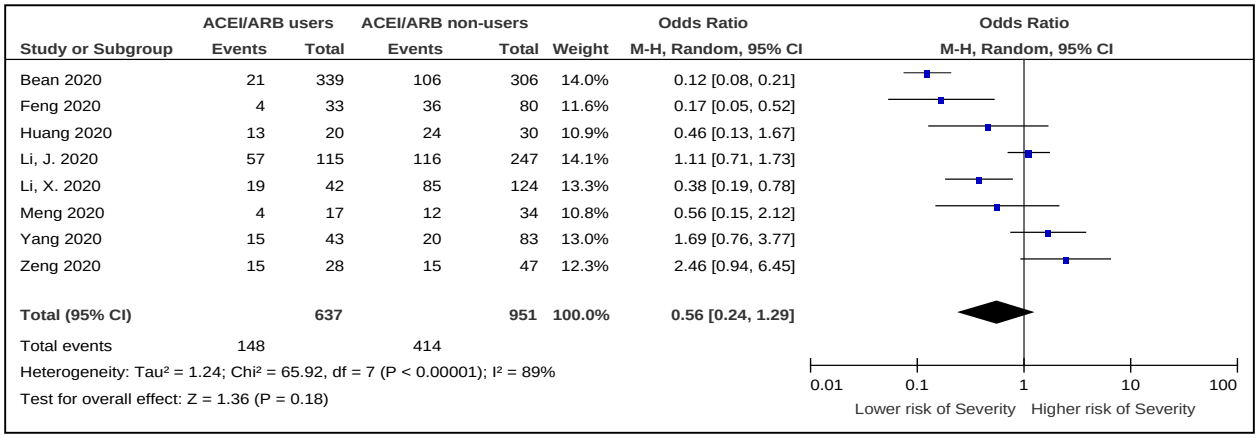

Figure 4. Forest plot for association of ACEI/ARB use with disease severity among hypertensive patients with confirmed COVID-19 infection.

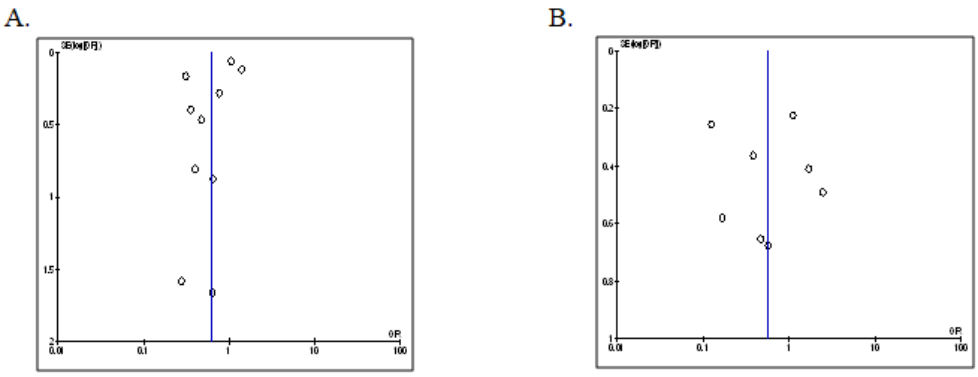

Figure 5. Funnel plots for association of ACEI/ARB use with: A) mortality; and b) disease severity.

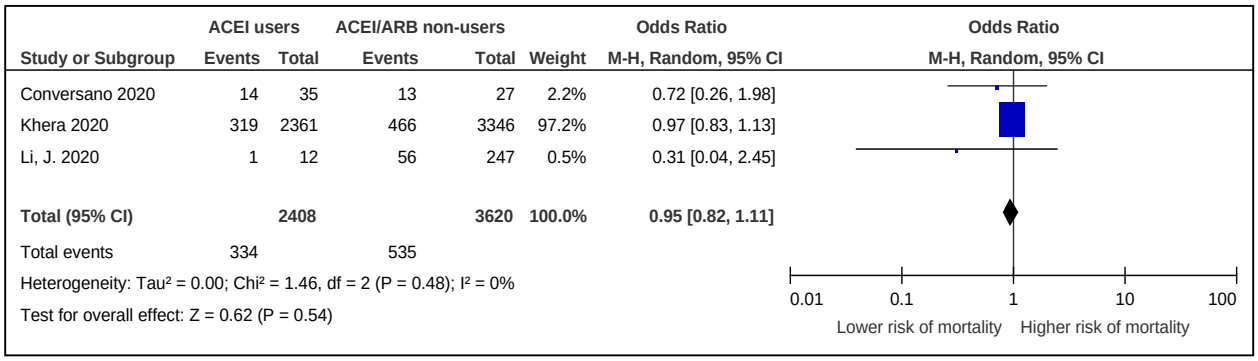

Figure 6a. Subgroup analysis among ACEI users and mortality among hypertensive patients with confirmed COVID-19 infection.

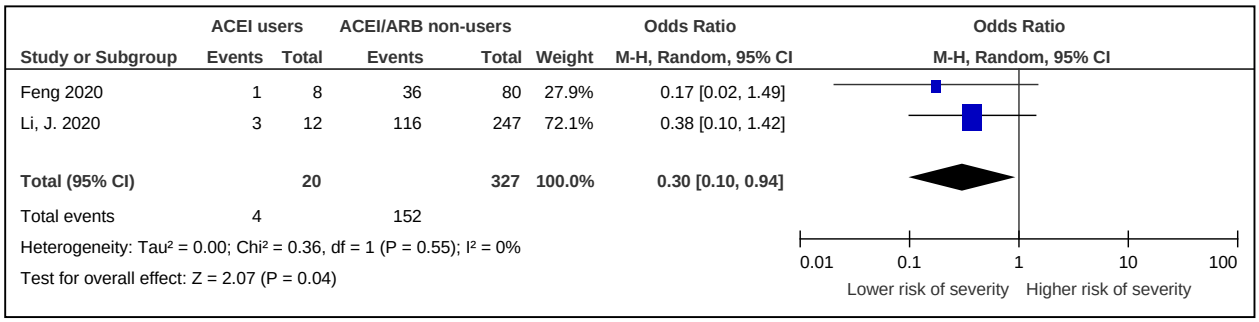

Figure 6b. Subgroup analysis among ACEI users and disease severity among hypertensive patients with confirmed COVID-19 infection.

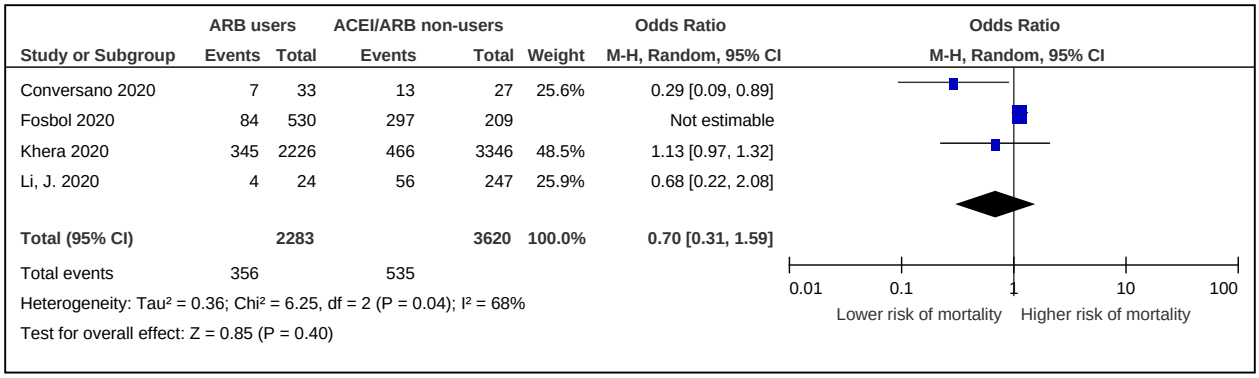

Figure 7a. Subgroup analysis among ARB users and mortality among hypertensive patients with confirmed COVID-19 infection.

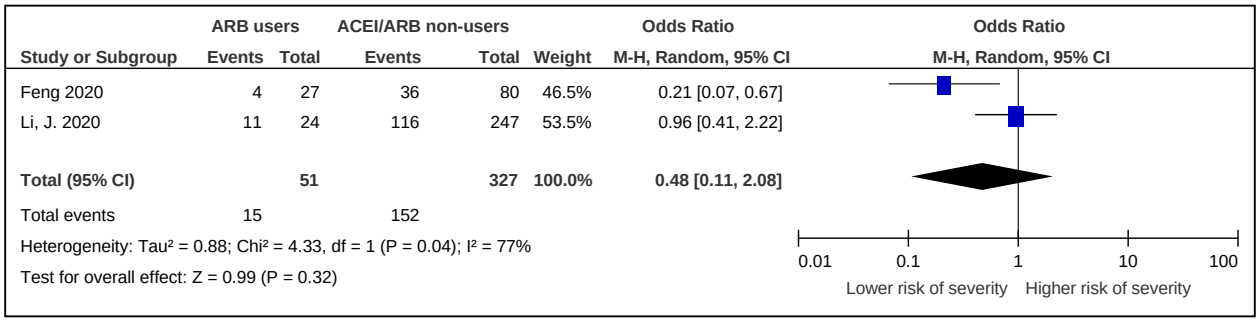

Figure 7b. Subgroup analysis among ARB users and disease severity among hypertensive patients with confirmed COVID-19 infection.

DISCUSSION

Across all the journals used in this meta-analysis, hypertension is one of the top co-morbidities of patients with confirmed COVID-19 infection, and ACEI and ARB seem to be popular choices for antihypertensive medications. The analyses done for both primary and secondary outcomes manifested decreased frequency of mortality and disease severity with ACEI/ARB use. The calculated odds ratio for mortality and disease severity were 0.63 (0.40, 0.99), and 0.56 (0.24, 1.29), respectively, at 95% confidence interval. Both had a value of less than 1,

hence pointing towards decreased frequency of both primary and secondary outcomes with ACEI/ARB use. However, the X^2 test and I_2 statistic revealed presence of statistically significant heterogeneity among the sample populations used in both outcomes. This signifies presence of confounding variables which should be identified and eliminated. Different study duration, monitoring of treatment outcome, prior history of RAAS inhibitors, varying exposure (i.e. dosage, drug frequency, duration of use) to RAAS inhibitors, and using other types of antihypertensive medications together with ACEI and ARB use are only some of the possible confounders which may have been present in the sample populations used. In addition, most of the articles came from Asia, specifically, China, which is not surprising since China is one of the countries with first reported cases of COVID-19 infection. To eliminate selection bias in the sample populations used, it would be better if there will be multiple studies involving other races with same baseline characteristics. Furthermore, using retrospective and observational studies already implicate selection bias due to the nature of the study. Hence, randomized controlled trials are encouraged. Lastly, both Funnel plots shown in Figure 5 indicate publication bias due to asymmetrical appearance of both graphs.

In the subgroup analysis done among the ACEI users versus ACEI/ARB non-users, Figure 6a and 6b showed a decreased frequency of mortality (odds ratio of 0.95 (0.82, 1.11), with an I^2 of 0% (P = 0.48)) and disease severity (odds ratio of 0.30 (0.10, 0.94), with an I^2 of 0% (P = 0.55)), respectively. This pertains to a statistically significant reduction for both outcomes with ACEI use without an issue on heterogeneity among the subpopulations used. On the other hand, the subgroup analysis done among ARB users versus ACEI/ARB non-users, also showed decreased frequency on both outcomes, however, there is a statistically significant heterogeneity existing in the subpopulations used. The computed odds ratios among ARB users versus ACEI/ARB non-users

were 0.70 (0.31, 1.59) (I^2 of 68% (P = 0.04)) and 0.48 (0.11, 2.08) (I^2 of 77% (P = 0.04)) for mortality and disease severity, respectively. Thus, like in the primary analysis done, the heterogeneity within the ARB users also signify confounding variables which must be eliminated to arrive at a superior conclusion.

CONCLUSION

In a short span of time, researches of the possible association of ACEI and ARB with mortality and disease severity of hypertensive patients with confirmed COVID-19 infection continue to emerge. Zhang, X. *et al*[13] concluded a lower risk of mortality with ACEI/ARB use and suggests continuation of use ACEI and ARB for hypertension. In this updated meta-analysis, there was noted decrease of mortality and disease severity with ACEI/ARB use, however, significant heterogeneity among the sample populations exists. Confounding variables must be identified and eliminated. Furthermore, subgroup analyses among ACEI users versus ACEI/ARB non-users, and ARB users versus ACEI/ARB non-users also manifested decrease of both outcomes. However, significant heterogeneity exists among the ARB users, which is in contrary among the ACEI users. Hence, we can conclude that ACEI use contributes to a statistically significant reduction of mortality and disease severity among hypertensive patients with confirmed COVID-19 infection. Such statement is aligned with the findings of Pirola and Sookoian[14] which stated that the use of ACEI contributed to ~35% reduction in the risk of death or critical disease, suggesting beneficial effect of ACEI use.

The authors of this study recommend continuing analysis of the possible effect of ACEI and ARB on clinical outcome of hypertensive patients with confirmed COVID-19 infection since recent analysis suggest a beneficial effect. More studies, preferably randomized controlled trials

must be done to explore beneficial effect of using ACEI and/or ARB among our hypertensive patients with COVID-19 infection. At present, our findings are still in line with the current recommendation to not discontinue the use of ACEI and ARB among our hypertensive patients.

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APPENDIX

Table 2. Number of ACEI/ARB users and ACEI/ARB non-users with Mortality as outcome.

Study	No. of Hypertensive Patients with Confirmed COVID-19 infection	ACEI/ARB users	Mortality among ACEI/ARB users	ACEI/ARB Non-users	Mortality among ACEI/ARB Non-users
Bean, D.M. *et al*	645	339	106	306	182
Conversano, A. *et al*	96	69	21	27	13
Huang, Z. *et al*	50	20	0	30	2
Ip, A. *et al*	1584	460	137	1124	262
Khera, R. *et al*	7933	4587	664	3346	466
Li, J. *et al*	362	115	21	247	56

Meng, J. *et al*	51	17	0	34	1
Yang, G. *et al*	126	43	2	83	9
Zeng, Z. *et al*	75	28	2	47	5
Zhang, P *et al*	1128	188	7	940	92

Table 3. Number of ACEI/ARB users and ACEI/ARB non-users with Disease Severity as outcome.

Study	No. of Hypertensive Patients with Confirmed COVID-19 infection	ACEI/ARB users	Severe/Critical Status among ACEI/ARB users	ACEI/ARB Non-users	Severe/Critical Status among ACEI/ARB Non-users
Bean, D.M. *et al*	645	339	21	306	106
Feng, Y. *et al*	113	33	4	80	36
Huang, Z. *et al*	50	20	13	30	24
Li, J. *et al*	362	115	57	247	116
Li, X. *et al*	166	42	19	124	85
Meng, J. *et al*	51	17	4	34	12
Yang, G. *et al*	126	43	15	83	20
Zeng, Z. *et al*	75	28	15	47	15

Table 4a. Number of ACEI users and ACEI/ARB non-users with Mortality as an outcome for subgroup analysis.

Study	No. of Hypertensive Patients with Confirmed COVID-19 infection	ACEI users	Mortality among ACEI users	ACEI Non-users	Mortality among ACEI/ARB Non-users
Conversano, A. *et al*	96	35	14	27	13
Khera, R. *et al*	7933	2361	319	3346	466
Li, J. *et al*	362	12	1	247	56

Table 4b. Number of ACEI users and ACEI/ARB non-users with Disease Severity as an outcome for subgroup analysis.

Study	No. of Hypertensive Patients with Confirmed COVID-19 infection	ACEI users	Severe/Critical Status among ACEI users	ACEI/ARB Non-users	Severe/Critical Status among ACEI/ARB Non-users
Feng, Y. *et al*	113	8	1	80	36
Li, J. *et al*	362	12	3	247	116

Table 5a. Number of ARB users and ACEI/ARB non-users with Mortality as an outcome for subgroup analysis.

Study	No. of Hypertensive Patients with Confirmed COVID-19 infection	ARB users	Mortality among ARB users	ACEI Non-users	Mortality among ACEI/ARB Non-users
Conversano, A. *et al*	96	33	7	27	13
Khera, R. *et al*	7933	2226	345	3346	466
Li, J. *et al*	362	24	4	247	56

Table 5b. Number of ARB users and ACEI/ARB non-users with Disease severity as an outcome for subgroup analysis.

Study	No. of Hypertensive Patients with Confirmed COVID-19 infection	ARB users	Severe/Critical Status among ARB users	ACEI/ARB Non-users	Severe/Critical Status among ACEI/ARB Non-users
Feng, Y. *et al*	113	27	4	80	36
Li, J. *et al*	362	24	11	247	116