# Mortality, Severity, and Hospital Admission Among COVID-19 Patients with ACEI/ARB Use: A Meta-analysis Stratifying Countries Based on Response to the First Wave of the Pandemic

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**Systematic Review**

**Keywords:** angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, Covid-19, mortality, disease severity, hospital admission

**Posted Date:** September 17th, 2020

**DOI:** https://doi.org/10.21203/rs.3.rs-75674/v1



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**Version of Record:** A version of this preprint was published at Healthcare on January 28th, 2021. See the published version at https://doi.org/10.3390/healthcare9020127.

# Abstract

### Background

The use of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) is controversial for treating COVID-19 patients. We aimed to estimate pooled risks of mortality, disease severity, and hospitalization associated with ACEI/ARB use and stratify them by country and country clusters.

### Methods

We conducted a search in various databases through 7/4/2020 and then applied random-effects models to estimate pooled risks (ORp) across stratifications by country cluster. Clusters were chosen to reflect outbreak times (China followed by Korea/Italy, others subsequently) and mobility restrictions (China and Denmark/France/Spain with stricter lockdowns than the UK/US).

### Results

Overall analysis showed no increase in mortality; however, a statistical increase in mortality was seen in the US/UK cluster with ORp=1.28[95%CI=1.04; 1.56] and a decrease in China with ORp=0.65[95%CI=0.43; 0.96] and France with OR=0.31[95%CI=0.14; 0.69]. Severity and hospitalization were not statistically significant in the analysis; however, several associations were seen in specific countries but not in country clusters.

### Conclusion

The country-cluster meta-analysis provided a reasonable explanation for COVID-19 mortality among ACEI/ARB users. The analysis did not explain differences in severity and suggested the involvement of other factors. Hospitalization findings may be considered informative as they may have been subjected to clinical decisions and hospital-bed availability.


# Background

Scientists have attempted to model the impact of non-pharmaceutical interventions (NPIs) on the global pandemic caused by the coronavirus beginning in 2019. NPIs may include contact tracing, increased testing, social distancing, and extreme measures such as complete lockdowns and banning public gatherings [1]. The most extreme example of an NPI was the national lockdown in Europe that included Italy, Spain, France, and Denmark, among other EU nations, and in China, which aimed to change the trajectory of the pandemic. This strategy was shown to be effective in reducing the time-varying reproduction number (Rt) of COVID-19 – “an epidemiological quantity that represents the average number of infections generated at time (*t)* by each infected case over the course of their infection” – almost

immediately after implementation [1]. By contrast, given the adverse economic impact of such strategies, few countries adopted the “herd immunity” strategy during the pandemic or imposed a delayed implementation of the lockdown [2, 3]. The literature suggests that low levels of national preparedness and governmental responses can increase the likelihood of an overwhelmed healthcare system that could result in adverse health outcomes for the most vulnerable patients in a society [4].

With the recent concern regarding angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB), there has been speculation that their use could increase the risk of exacerbating COVID-19 infections by upregulating ACE2 expression [5, 6 ]. However, it has also been hypothesized that these could yield favorable outcomes [7]. These conflicting opinions are supported by published human studies, as we will discuss in this study.

Interestingly, many diseases such as hypertension, diabetes, renal, and cardiovascular diseases share a common indication for ACEI/ARB [5]. Among other factors, the association of ACEI/ARB with increased risk of COVID-19 requires further evaluation in this subset of vulnerable patients [5].

Beyond the theoretical in these patients, we attempted to evaluate whether or not specific countries and country clusters were successful in mitigating the risk of worse COVID-19 outcomes in ACEI/ARB users compared to non-ACEI/ARB users during their first wave of the pandemic. The results of this study would help to explain several of the discrepancies seen in COVID-19 outcomes associated with ACEI/ARB in the published literature. Therefore, our primary objective was to estimate the pooled risks of mortality and disease severity associated with ACEI/ARB use and then stratify these by country and country clusters. Exploratorily, we also estimated the pooled risk of hospitalization with due caution because of factors independent of COVID-19.

# Methods

We complemented an amended [8] meta-analysis and a living systematic review [9, 10] with an updated search through 7/4/2020 in the PubMed, Cochrane, and medRxiv.org databases. A PRISMA flowchart is shown in Figure S1 in the supplementary section. The following is the modified population, intervention, comparison, outcome, study type (PICOS) criteria[11]: 1) Population: patients of any age who tested positive for COVID-19; (2) intervention: ACEI or ARB; (3) comparison: no ACEI or ARB (4) outcomes: mortality, disease-severity, and hospital admission; (5) study type: observational, cohort, case-control, controlled and non-controlled. Studies published a language other than English were excluded. The Quality assessment was carried out using  the Newcastle–Ottawa Scale (NOS) [12].

Two authors (AAA; ASA) screened publications and extracted odds ratios (OR). For studies not reporting ORs but including adequate data, we estimated the crude OR. Using R Core Team (2020) software (R Foundation for Statistical Computing, Version 4.0.1, Vienna, Austria), we applied random-effects models to estimate pooled risks ($OR_p$) across all studies and stratified by studies with and without statistical adjustment, Q-test and $I^2$ to quantify heterogeneity, and funnel plots and Egger’s test to assess

publication bias. We performed sensitivity meta-regression analyses by country and country clusters. The clusters were chosen to reflect time of outbreaks (China first, Korea/Italy next, others subsequently) and mobility restrictions (China and Denmark/France/Spain with stricter lockdowns than the UK/US).

# Results

Thirty publications reporting *k*=61 mortality, disease-severity, and/or hospitalization analyses were included (Table S1 and Figure S1 in the supplementary section). The $OR_p$ for mortality (*k*=24) was statistically non-significant at 0.86 (95%CI=0.68–1.08), remaining non-significant when stratified by adjustment and in sensitivity analyses by country and country clusters, except for China and France, where a decrease was seen, and the UK/US cluster, where an increase in mortality risk in association with ACEI/ARB exposure were observed (Table 1; Figure 1 and Figure 2). The $OR_p$ for COVID-19 disease severity (*k*=30) was 0.92 (95%CI=0.74–1.15) and remained statistically non-significant when considering adjusted studies only.

The single French study reported a statistically significant increase, while the one British study related a significant decrease in severe COVID-19 disease risk in association with ACEI/ARB use. The remaining sensitivity analyses yielded non-significant results. The $OR_p$ for hospitalization (*k*=7) was 1.17 (95%CI=0.78–1.75) and remained statistically non-significant in studies with adjustment but not in those without adjustment. The association of ACEI/ARB use and hospitalization risk was non-significant for China and Italy but significant for the US. Heterogeneity was low ($I^2$<30%=11) to moderate ($I^2$30%–60%=8) with some high ($I^2$>60%=4). Funnel plots and Egger's tests were significant for mortality (p=0.04) but not for disease severity (p=0.216) and hospitalization (p=0.337), as shown in Figure S2.

# Discussion

With a verifiable total of 43,829 patients in the analysis, including 11,166 exposed to ACEI/ARB, our meta-analysis consistently revealed the absence of an association between ACEI/ARB use and mortality, disease severity, and hospitalization risk in COVID-19, a finding to be validated as further evidence accumulates. The country cluster sensitivity analysis explained several of the differences seen in the mortality outcome. The UK/US cluster revealed an increased risk of mortality with two of the three studies [13,14] having OR adjusted for comorbidities. The study by Richardson et al. was a large case series in New York conducted between March 1 and April 4, 2020, dates that coincide with that state's first wave of the pandemic prior to extreme measures such as stay-at-home orders being taken [15,16]. A similar pattern emerges with the UK study by Bean et al. in which the country experienced their first wave prior to lockdown measures [1, 14, 17, 16]. Studies in France, Italy, China, Denmark, Spain and Korea were also conducted in their first wave; however, in contrast, during that time they had already implemented multiple NPI strategies (including a national lockdown) to mitigate the impact of the pandemic [1, 18, 19]. Based on our analysis, two of these countries (France and China) saw a decrease in mortality among ACEI/ARB users (shown in Figure 2). It would be difficult to determine whether this effect was due to an underlying

mechanism of ACEI/ARB protection or if it was the result of very strict NPIs having been executed. With cautious interpretation, among many other factors, this may suggest that countries with much stricter NPI policies may have been successful in reducing mortality among ACEI/ARB users suffering from COVID-19 in the early stages of the pandemic.

The meta-regression sensitivity analyses by country clusters did not explain the heterogeneity in the disease-severity endpoint very well. Indeed, harmonization of disease-severity definitions may strengthen future studies and meta-analyses; however, more importantly, some researchers suggest the existence of ACE-2 overexpression polymorphism as a potential explanation for the severity of the COVID-19 presentation [20]. The country-cluster analysis is not well-suited to answer this question, and more studies among different ethnic groups are needed. For example, in a large cohort in the UK, it was found that Blacks being treated with ACEI/ARB were more susceptible to COVID-19 compared to Whites [21]. Whether this ethnic difference is real is yet to be determined, and the discordant country-specific results are points for future attention as more data start to accumulate. Lastly, the sensitivity analysis by country revealed more hospitalizations in the US among ACEI/ARB users. We believe that the hospitalization findings should be considered informative, at best, as these are influenced by clinical decisions and hospital-bed availability and not based on objective criteria.

An advantage of this current analysis is that we captured published studies from early stages of the pandemic in each country. Therefore, we think that we were able to estimate the risk of mortality during the implementation of NPI measures (especially national lockdowns) in a number of countries. The South Korean national response was a highly successful model for handling the pandemic. With aggressive measures that included contact tracing to prevent community transmissibility, South Korea reported the largest numbers of cases in the first two months of the pandemic. Among other factors, these large numbers of cases did not translate into increased mortality among ACEI/ARB users [19].

# Conclusion

In summary, our meta-analysis of studies accrued to 7/4/2020 suggests no evidence of an association of ACEI/ARB exposure with mortality, COVID-19 disease severity, or hospitalization. The country-cluster meta-analysis provided a reasonable explanation for differences in the mortality outcome, while it failed to explain the severity outcome. More studies of ACEI/ARB and COVID-19 severity outcomes in different populations are needed. The association of ACEI/ARB with mortality outcomes may be related in part to waves of infection; non-pharmaceutical measures such as mobility restrictions, contact tracing, and increased testing, and progress in therapeutic treatments.

# Abbreviations

NPIs: non-pharmaceutical interventions
COVID-19: novel coronavirus

Rt: reproduction number

t: time

ACEI: Angiotensin-converting enzyme inhibitors

ARB: Angiotensin-receptor blockers

ACE2: Angiotensin-converting enzyme-2

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

NOS: Newcastle–Ottawa Scale
OR: Odds ratio
ORp: Pooled odds ratio
CI: Confidence Interval

# Ethics Declaration

### Ethics approval and consent to participate

Not applicable

### Consent for publication
Not applicable

### Competing interests

The authors have no financial or other beneficial interests related to the work reported herein to declare.


### Funding

This work received no financial support or funding by any agency or organization.


### Author Contributions

Conceptualization: I.A., and A.A.A.; methodology: A.A.A.; software: A.A.A.; formal analysis: A.A.A.; data curation: A.A.A, A.S.A., and A.A.; writing: A.A.A., I.A, A.S.A, and A.A.; manuscript review and editing: I.A, A.A. and A.S.A.; visualization: A.A.A., and A.S.A.

### Availability of data and materials
The datasets supporting the conclusions of this article are included in the supplementary content.


### Acknowledgement

Authors will like to thank Prince Sattam Bin Abdulaziz University, University of Arizona, King Faisal University, and King Fahad Medical City for their continued support for academic publishing.

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# Tables

**Table 1.** Overall and stratified pooled risk estimates for mortality, severity, and hospitalization[1]

| | Studies[2] | $OR_p$ [95%CI][3] | $I^2$ (if $k \geq 2$) |
|---|---|---|---|
| **Mortality** | | | |
| All reports[4] | 24 | 0.86 [0.68; 1.08] | 41% |
| *Adjusted* | 11 | 0.81 [0.65; 1.02] | 0% |
| *Unadjusted*[5] | 13 | 0.91 [0.61; 1.35] | 50% |
| By country / cluster | | | |
| *China* | 11 | 0.65 [0.43; 0.96] | 0% |
| *Korea* | 1 | 0.88 [0.53; 1.45] | - |
| *Italy* | 5 | 1.03 [0.71; 1.46] | 29% |
| *Denmark* | 1 | 0.83 [0.67; 1.03] | - |
| *France* | 1 | 0.31 [0.14; 0.69] | - |
| *Spain* | 2 | 0.58 [0.19; 1.81] | 0% |
| *UK* | 1 | 1.23 [0.93; 1.62] | - |
| *US* | 2 | 1.32 [0.99; 1.75] | 0% |
| *Korea/Italy* | 6 | 1.00 [0.74; 1.36] | 15% |
| *Denmark/France/Spain* | 4 | 0.60 [0.35; 1.03] | 50% |
| *UK/US* | 3 | 1.28 [1.04; 1.56] | 0% |
| **Severity** | | | |
| All reports[4] | 30 | 0.92 [0.74; 1.15] | 64% |
| *Adjusted* | 20 | 0.92 [0.74; 1.16] | 59% |
| *Unadjusted*[5] | 10 | 0.90 [0.61; 1.33] | 67% |
| By country / cluster | | | |
| *China* | 14 | 0.74 [0.50; 1.10] | 54% |
| *Italy* | 5 | 0.74 [0.49; 1.11] | 40% |
| *Denmark* | 1 | 1.15 [0.94; 1.40] | - |
| *France* | 1 | 2.28 [1.17; 4.43] | - |
| *Spain* | 2 | 1.13 [0.67; 1.91] | 0% |
| *UK* | 1 | 0.63 [0.47; 0.84] | - |
| *US* | 6 | 1.27 [0.96; 1.66] | 73% |
| *Denmark/France/Spain* | 4 | 1.30 [0.91; 1.87] | 24% |
| *UK/US* | 7 | 1.15 [0.84; 1.56] | 81% |
| **Hospitalization** | | | |
| All reports[4] | 7 | 1.17 [0.78; 1.75] | 46% |
| *Adjusted* | 6 | 1.29 [0.94; 1.77] | 31% |
| *Unadjusted*[5] | 1 | 0.38 [0.12; 2.91] | - |
| By country | | | |
| *China* | 1 | 0.38 [0.12; 1.25] | - |
| *Italy* | 3 | 1.04 [0.66; 1.65] | 0% |
| *US* | 3 | 1.56 [1.17; 2.07] | 0% |

[1] Patients (ACEI/ARB vs non-ACEI/ARB) in analyses: mortality: 4145 vs 14996; severity: 8168 vs 28976; hospitalization: 1374 vs 8138 (numbers are approximate because of inconsistent reporting).

[2] Number of studies included in the meta-analysis. Studies with separate estimates for both ACEI and ARB are counted separately.

[3] Random effect models were used for all analyses. $OR_p$ was estimated if

≥2 studies and OR if only 1 study in the analysis.

[4] Combined analysis of adjusted and unadjusted odds ratios.

[5] Crude OR calculated for studies reporting adequate data.

Abbreviations

ACEI: angiotensin-converting enzyme inhibitors

ARB: angiotensin II receptor blockers

CI: confidence interval

*k*: number of studies in analysis

OR: odds ratio

$OR_p$: pooled odds ratio

# Figures

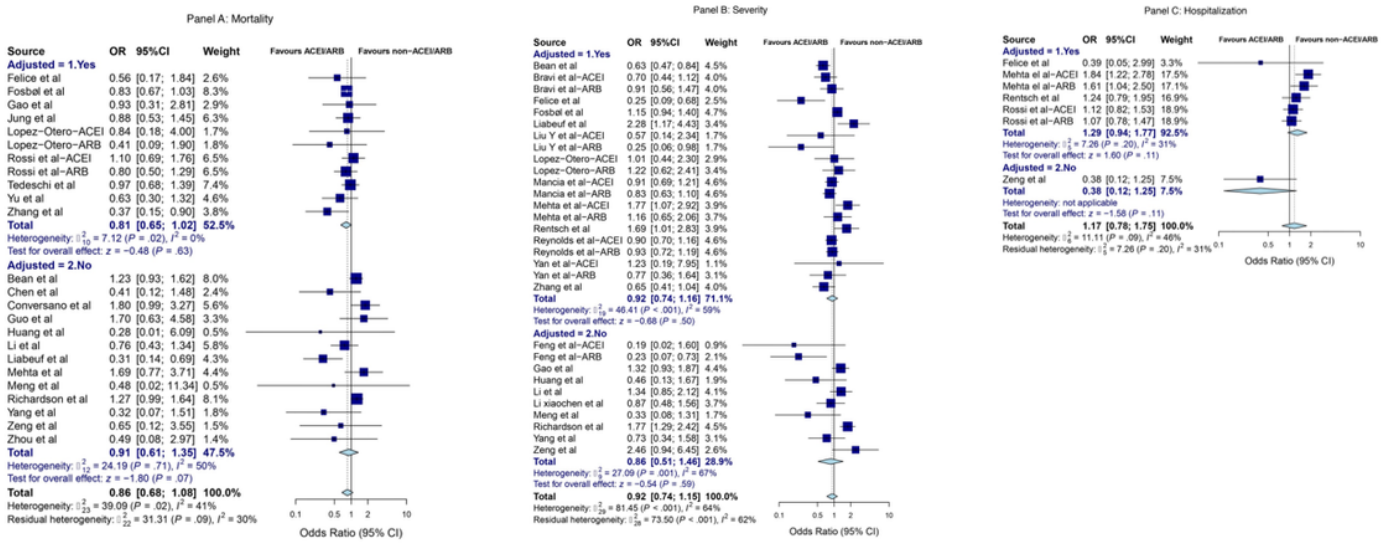


**Figure 1**

Forest plots for (A) mortality, (B) severity of COVID-19 disease, and (C) hospitalization. All studies were published in 2020. The size of squares is proportional to the weight of each study. Horizontal lines indicate the 95% CI of each study; diamonds indicate the pooled estimate with 95% CI. Abbreviations: CI: confidence interval; OR: odds ratio. ACEI: Angiotensin-converting enzyme inhibitors. ARB: Angiotensin II receptor blockers.

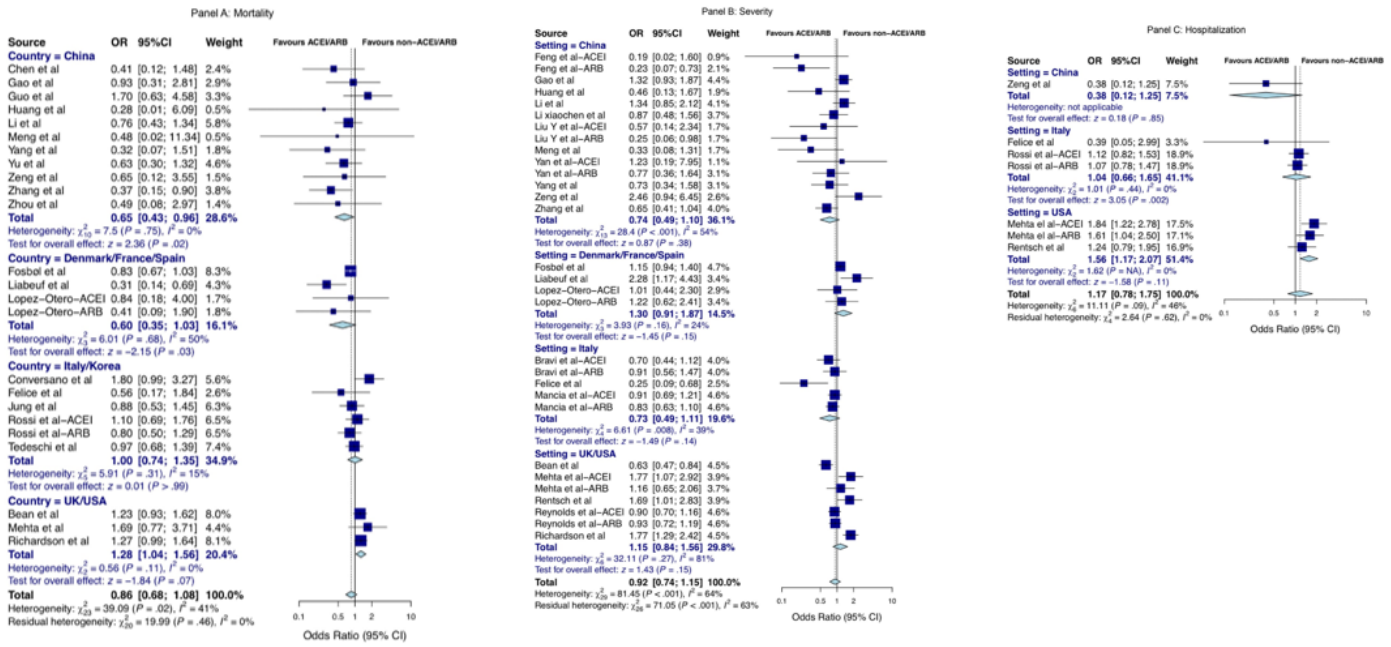


**Figure 2**

Forest plots for country clusters (A) mortality, (B) severity of COVID-19 disease, and (C) hospitalization. All studies were published in 2020. The size of squares is proportional to the weight of each study. Horizontal lines indicate the 95% CI of each study; diamonds, the pooled estimate with 95% CI. Abbreviations: CI: confidence interval; OR: odds ratio. ACEI: Angiotensin-converting enzyme inhibitors. ARB: Angiotensin II receptor blockers.

# Supplementary Files

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