ORIGINAL ARTICLE

# IMPACT OF HYPERTENSION ON COVID-19 MORTALITY RATE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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## ABSTRACT

**Introduction:** As the WHO has declared that Coronavirus Disease 2019 (COVID-19) is a global emergency, clinical predictors of severity must be identified to optimize the treatment. Hypertension is the most prevalent comorbidity. It has been commonly reported that it increases the mortality rate, although some research has shown conflicting results. This study aims to measure some literature on the correlation between hypertension and mortality rate in COVID-19.
**Methods:** This study is a meta-analysis. The research was conducted using secondary data by searching and selecting clinical studies. The article searching was through a systematic and comprehensive database from PubMed, Science-Direct, Google Scholar, ProQuest, and Springer Link. Articles were collected using the PRISMA diagram, critically appraised using the PRISMA checklist and PICO analysis, then the data were analyzed using Review Manager 5.4.1 application with Random Effect Model (REM). The analysis results are the effect size, heterogeneity, and the study model.
**Results:** Based on the meta-analysis from the five included studies, the hypertension group had a 2.76-fold higher risk of mortality (RR 2.76, 95% CI 2.58-2.96) caused by COVID-19 compared to the group without hypertension. I2 statistics showed heterogeneities among the included studies, and hence the random effect model is used. Funnel plots were plotted for the included studies in the meta-analysis, which suggested a publication bias in the studies of our meta-analysis.
**Conclusion:** COVID-19 patients with hypertension are associated with a higher risk of COVID-19 mortality rate.
**Keywords:** Hypertension, COVID-19, Mortality rate.

## INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is a pandemic that began in Wuhan (Hubei, China) and has been declared as a public health emergency by the World Health Organization (WHO).[1] Weekly COVID-19 case incidence peaked on the 29th of November to the 5th of December 2021, with over 4 million confirmed new cases recorded and weekly mortality rising 10% from the previous week with over 52.500 new deaths reported. Globally, almost 265 million confirmed cases and over 5.2 million fatalities had been reported as of the 5th of December.[2]
Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the agent that causes this disease by entering cells via the Angiotensin-Converting Enzyme 2 (ACE2) receptor.[3] This enzyme catalyzes the conversion of angiotensin II to angiotensin 1–7, a peptide that counteracts angiotensin II's pro-inflammatory, pro-oxidative, vasoconstrictive, and fibrotic effects.[4] Because of the link between SARS-CoV-2 and ACE2 receptors, hypertension may have a role in viral infection susceptibility and COVID-19 severity.[5]
In general, hypertension is the most prevalent comorbidity in COVID-19 patients.[6] In a 1.099 severe COVID-19 patients study, hypertension was also the most common comorbidity (23%).[7] Despite widespread media coverage suggesting hypertension raises the risk of severe COVID19, several early studies showed no link between hypertension and disease severity.[8–12] Therefore, the purpose of this article is to measure some of the literature on how hypertension affects the mortality rate of COVID-19 patients.

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## METHODS

### Search and study selection

This study is a systematic review and meta-analysis. This study used data collected through the PubMed, ScienceDirect, Google Scholar, ProQuest, and SpringerLink databases using the keywords (Impact OR Correlation OR Relationship) AND (Comorbidity Hypertension) AND (mortality rate) AND (COVID-19 OR Coronavirus OR SARS-CoV-2).

### Inclusion Criteria

Articles that meet the inclusion criteria in this study are those published during 2020 and 2021, including observational studies in the form of primary studies conducted in hospitals. Adult patients diagnosed with COVID-19 were used as research subjects. Only articles in English are included. These articles are articles that discuss the impact of hypertension on COVID-19 mortality rate.

### Exclusion Criteria

This study excluded articles with randomized control trial design, quasi-experimental, case-control, articles that were not published in English, as well as studies involving others outcome and data were not reported as mean or number subject.

### Data extraction and analysis

The articles were collected using the the PRISMA diagram. After that, the four authors carried out a critical study using Quality Assessment Tools for Observational Cohort and Cross-Sectional Studies NIH (National Institutes of Health) and PICO analysis. Then the data were analyzed using Review Manager 5.4.1 (RevMan 5.4.1) with Random Effect Model (BRAKE). The results obtained include effect size, heterogeneity, and study model.

## RESULTS

The initial search process through the database resulted in 345 articles. After eliminating duplicate articles, 340 articles were excluded for the following reasons: irrelevant articles (n=243) articles without full text (n=24), randomized controlled trials (n=2), meta-analysis (n=30), systematic review (n=22), and do not speak English (n=2). Nine full-text articles were assessed for eligibility; four were excluded because study outcomes were not mortality rates. A total of 5 studies were found to meet the inclusion criteria. Studies that meet the inclusion criteria are then assessed for quality quantitatively and qualitatively. Quality assessment in this study was carried out using the Quality Assessment Tools for Observational Cohorts and Cross-Sectional Studies published by the NIH (National Institutes of Health). The risk of bias of the included studies was evaluated using a modified version of the Quality in Prognostic Studies (QUIPS) tool

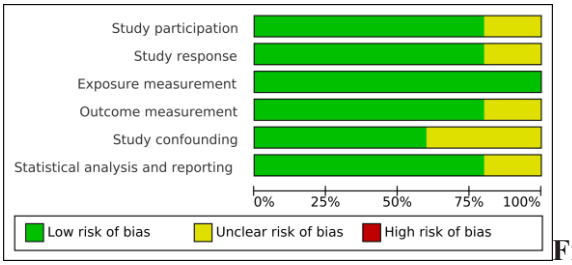


**Figure 1**. Risk of bias assessment

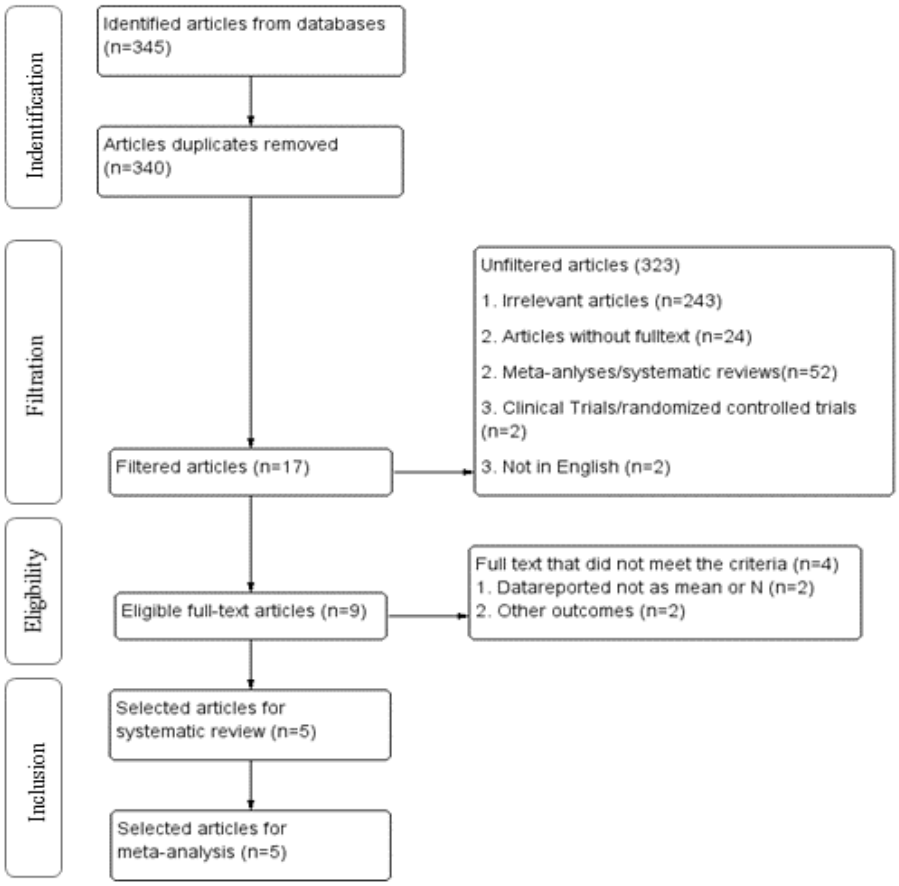


**Figure 2.** Research steps with PRISMA flow diagram

**Table 1.** Characteristics of the included studies

| Author (year) | Country | Type | Sample | Hypertension | | Study Quality Index |
|---|---|---|---|---|---|---|
| | | | | HT (%) | Deaths (%) | |
| Augusto (2020) | Italy | Cross sectional | 3894 patients with SARS-CoV-2 infection hospitalized from February 19th to May 23rd, 2020 | 1943 (49) | 461 (23) | 8 |
| Chanyuan (2020) | China | Cross sectional | 856 patients diagnosed with COVID- 19 from 17 January to 7 February 2020, | 142 (16) | 1 (0.7) | 7 |
| Diego (2020) | Mexico | Cross sectional | 212,802 cases of laboratory-confirmed COVID-19 | 42,453 (20) | 10,942 (26) | 9 |
| Gaspar (2020) | Mexico | Cross sectional | 331,298 positive cases of COVID-19 | 66,170 (20) | 16,409 (24) | 9 |
| Guido (2020) | Italy | Cross sectional | 1761 patients aged 18 to 101 years with confirmed COVID-19, | 873 (49) | 137 (15) | 8 |

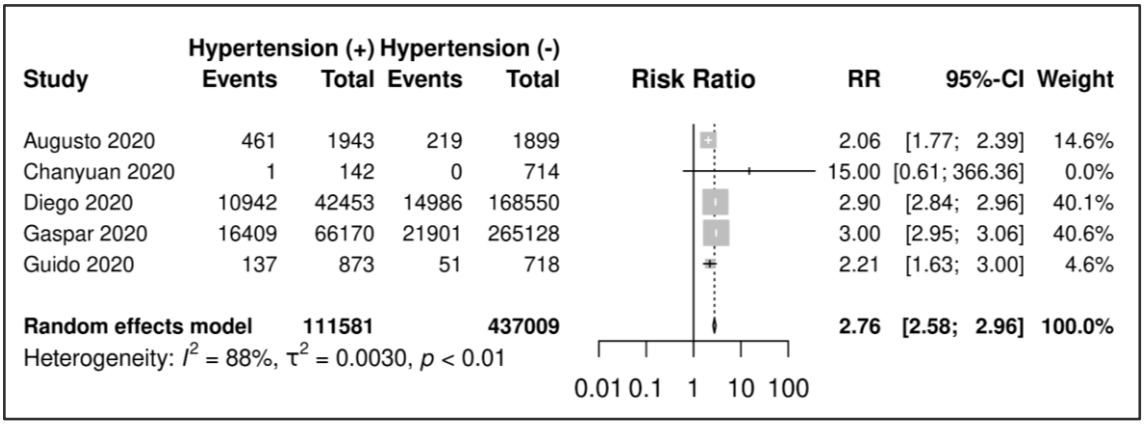


**Figure 3.** Meta-analysis of the impact of hypertension on COVID-19 mortality rate.

Based on the meta-analysis from the 5 included studies, the hypertension group had a 2.76-fold higher risk of mortality (RR 2.76, 95% CI 2.58-2.96) caused by COVID-19 than the group without hypertension. $I^2$ statistics showed heterogeneities (88%) among the included studies; hence the random effect model is used. Funnel plots were plotted for the included studies in the meta-analysis, which suggested a publication bias in the studies of our meta-analysis.

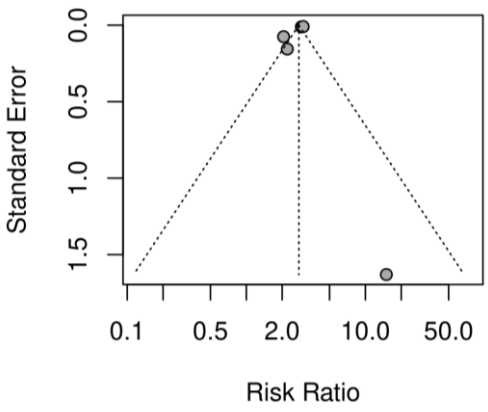


**Figure 4.** Funnel plot for detection of publication bias

## DISCUSSION

This meta-analysis was based on five observational studies of confirmed COVID-19 patients worldwide. Our result suggests that hypertension morbidity in COVID-19 patients increased their mortality rate (RR: 2.76; 95% CI 2.58-2.96). The early report from 138 cases of COVID-19 in Wuhan describes that 46.4% of patients had one or more comorbidities with hypertension (31.2%) as the most common comorbidity present, followed by diabetes (10.1%), cardiovascular disease (14.5%), and malignancy (7.2%).[13] It also suggested that these patients are also likely to be admitted to the intensive care unit.[13] Furthermore, another study also concluded that underlying diseases such as hypertension, cardiovascular disease, and respiratory system disease are risk factors for developing severe COVID-19.[14]

In recent years, non-communicable diseases (NCDs) such as hypertension have become the main health issue worldwide and cause about 70% of deaths worldwide.[15] However, our concept toward diseases has shifted since the emergence of the COVID-19 pandemic, a communicable disease (CD), in 2020. The pandemic makes us realize that CDs can also change how we live and threaten many aspects of our life. Moreover, COVID-19 is closely related to hypertension since SARS-CoV-2, a virus that causes COVID-19 binds to angiotensin-converting enzyme 2 (ACE-2) as its functional receptor to infect the cells.[16] ACE-2 is one of the renin-angiotensin system (RAS) components that play a crucial role in controlling blood pressure and development of atherosclerotic plaque.[17] Therefore, there is a close relationship between SARS-CoV-2 and hypertension.

The exact mechanism that links COVID-19 and preexisting hypertension has not been fully understood. However, it may be caused by RAS imbalance and endothelial dysfunction.[18] Activation of the conventional RAS (ACE/Ang II/AT1 receptor) axis, together with down-regulation of the non-conventional RAS (ACE2/Ang 1-7/Mas receptor) axis was proposed as the underlying cause of severe COVID-19 outcomes in hypertensive patients.[19] Mechanical stress caused by elevated systemic pressure leads to premature aging, increased endothelial cells turnover, increased reactive oxygen species (ROS), a decrease of vasorelaxant agent

production, and vascular remodeling.[20-21] All these development leads to endothelial dysfunction. Endothelial dysfunction was also hypothesized to play a major role in the progression of COVID-19 because of the manifestations of hypercoagulability state among COVID-19 patients.[22]

The presence of hypertension in COVID-19 patients must be addressed and treated appropriately. Proper treatment will increase the survival of these patients. However, whether hypertension can predict mortality in COVID-19 patients is still debatable. One of the studies included in this meta-analysis conducted by Guido et al. reported that only age, diabetes mellitus, chronic obstructive pulmonary disease, and chronic kidney disease could be used to predict mortality in COVID-19 patients.[11]

We want to address the limitations of this meta-analysis. First, we used articles from around the world without any limitation in ethnicity, country, sample size, and research methods. Our study has a high heterogeneity statistic (88%). It might be caused by large variation among studies in the sample size (866 to 331,298 patients). Second, the difference in lengths of follow-up might miss the events leading to heterogeneity.

## CONCLUSION

Based on data analysis conducted on COVID-19 patients with comorbid hypertension, it can be concluded that the possibility of experiencing mortality in these patients were higher than in patients without hypertension (RR 2.76, 95% CI 2.58-2.96.).

Therefore, it is important to optimize blood pressure control in hypertensive patients and monitor carefully for complications during COVID-19 infection.

Further studies to determine optimal pharmacological therapy in COVID-19 patients with hypertension are needed to decrease the mortality rate in these patients.


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