

Hypertension in Associated with COVID-19

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Abstract

The novel coronavirus infection (COVID-19), now a worldwide public health concern is associated with varied fatality. Patients with chronic underlying conditions like hypertension have shown worst outcomes. Hypertension is a multifactorial disease and a public health burden, as it is a risk factor for diseases like stroke, coronary artery disease, and heart failure. As one of the most important public health problems in the 21st century, hypertension affects more than one billion individuals worldwide. Hypertension is a common comorbidity in COVID-19 patients. However, the association of hypertension with the severity and fatality of COVID-19 remain unclear. Hypertension is a major risk factor regarding the severity and fatality of COVID-19, and the RAAS plays an important role in COVID-19 infection since SARS-CoV-2 can lead to a dysregulation of the system by reducing the ACE2 expression. Hypertension may also affect the prognosis of COVID-19 illness. The severity rate of COVID-19 in hypertensive patients was much higher than in non-hypertensive cases. A systematic literature search was conducted using several databases on studies that assess hypertension and outcome in COVID-19. Composite of poor outcome, comprising of mortality, severe COVID-19, acute respiratory distress syndrome (ARDS), need for intensive care unit (ICU) care and disease progression were the outcomes of interest. Authors independently reviewed some titles, abstracts and read full-texts of articles to identify potentially eligible studies to decide about final inclusions. This systematic review was conducted based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Statement. We used six different databases: Pubmed, Clinical Key, Science Direct, Cochrane Library, Springer Link and Oxford Academic. A total of 2731 articles from the databases were identified, we got three articles that fulfill the criteria. We excluded the other studies by reading the title, abstract, and full text assessment. Hypertension was associated with the severity and mortality of COVID-19 illness. Hypertension was also independently associated with a significantly increased risk of critical COVID-19 and in-hospital mortality of COVID-19.

Keywords: Hypertension, corona, COVID-19, severity

1. Introduction

Coronavirus disease (COVID-19), first discovered in Wuhan in December 2019, is an acute respiratory infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). A previously unknown betacoronavirus was discovered through the use of unbiased sequencing in samples from patients with pneumonia. Human airway epithelial cells were used to isolate a novel coronavirus, named 2019-nCoV, which formed a clade within the subgenus sarbecovirus, Orthocoronavirinae subfamily. Different from both MERS-CoV and

SARS-CoV, 2019-nCoV is the seventh member of the family of coronaviruses that infect humans.¹ Coronaviruses are enveloped non-segmented positivesense RNA viruses belonging to the family Coronaviridae, broadly distributed in humans and other mammals.² Transmission routes of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) occurs primarily via respiratory droplets from face-to-face contact (eg, from coughing, sneezing, shouting) and, to a lesser degree, via contaminated surfaces on which the viruses resides. Transmission may also

occur via aerosols (smaller droplets that remain suspended in air).³

Corona Virus Disease 2019 (COVID-19) pneumonitis associated with severe respiratory failure carries a high mortality. Coagulopathy has emerged as a significant contributor to thrombotic complications.⁴ The clinical features of COVID-19 are varied, ranging from asymptomatic states or mild upper respiratory tract infections to severe pneumonia with respiratory failure (acute respiratory distress syndrome [ARDS]) in the early stages or even death.⁵ Generally, patients with COVID-19 disease experience similar symptoms of common cold and flu, whereas some of them never show any symptoms. Comorbidities, such as hypertension, have been reported to be significantly more frequent in COVID-19 patients treated in intensive care units (ICU).⁶ Symptoms are varied from fever, sneezing, cough, and shortness of breath to throat pain, pneumonia, and acute respiratory distress syndrome (ARDS).⁷ Cardiovascular diseases, in particular hypertension, as well as the cardiovascular treatment with Renin-Angiotensin System inhibitors such as Angiotensin Converting Enzyme (ACE) inhibitors and Angiotensin Receptor Blockers (ARBs), are claimed once again as mechanisms of Severe Acute Respiratory Syndrome (SARS) during the COVID-19 outbreak due to Cov-2 epidemics.⁸

Side effects and mortality are generally observed in old patients or patients with comorbid illnesses. Fatality rate in these patients is 50–75%; while this rate in adult patients is 4 to 11%. Overall, the fatality rate in COVID-19 patients is between 2 and 3%.⁹ Severity of disease in infants, children and young people has also been stated to be considerably slighter than the adult patients. Rarely, multiorgan dysfunction and pneumonia in children as well as mild

infection in the neonatal have been reported.¹⁰

There is about 15% of older adults or those with chronic diseases may progress to severe pneumonia, develop acute respiratory distress syndrome (ARDS), septic shock, and/or multiple organ failure, although a large proportion of patients with COVID-19 display mild to-moderate illness.¹¹ The most frequent comorbidity in patients with COVID-19 is hypertension and it has been identified as a major risk factor for the increased severity and mortality associated with COVID-19 based on epidemiological studies.¹² A study in 2020 that conducted by Pranata et al said that hypertension increased the likelihood of bad outcomes, such as the severity of infection, ARDS, and mortality in patients infected with COVID-19.¹³ Comparisons of COVID-19 patients with mild and severe clinical symptoms can be used to evaluate whether hypertension is a risk factor for aggravation of the disease.¹⁴ It has been reported that the presence of cardiovascular diseases, such as hypertension and heart disease, is associated with adverse outcomes and mortality in SARS patients.¹⁵

However, there are some factors that could potentially confound a possible relationship between hypertension and severe COVID-19. The first factor is age, both severe COVID-19 and hypertension are common in the elderly. In addition, the identified risk factors like diabetes, smoking history, heart failure, etc. are generally associated with aging and/or vascular disorders which are common in patients with hypertension. Therefore, the risk of developing severe COVID-19 is more likely to be due to underlying vascular endothelial dysfunction and/or organ damage than high blood pressure (BP).^{16,17}

Prevalence of hypertension in COVID-19 seems higher in patients with high severity, which includes the use of intensive care unit

or use of mechanical ventilation, ARDS, or death. There is 23.7% of subjects with hypertension as one of the coexisting illnesses had a more severe course of COVID-19 disease compared with 13.4% subjects, who had a nonsevere disease reported on study in China.¹⁸ A cohort study from China showed that there is like 58% of COVID-19 patients who required intensive care had hypertension, whereas only 21.6% of total COVID-19 patients who did not require the use of ICU had hypertension. However, these associations did not account for age in the analysis and may be confounded by the higher incidence of hypertension in older people.¹⁹ Currently, there are no vaccines or reliable treatments available for the prevention or treatment for CoV-2 infection; therefore, it is important to understand its mechanism of infection and higher risk among individuals with obesity, diabetes, and hypertension to possibly reduce the morbidity and associated mortality. Severe COVID-19 cases should be admitted to hospital as soon as possible. The combined regimens of three or more antiviral drugs might not be useful for viral clearance, and should be performed carefully and cautiously.²⁰

2. Method

2.1 Protocol and Registration

To perform this systematic review, the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement was used.

2.2 Eligibility Criteria

In this systematic analysis, all research studies of adult COVID-19 patients with information on hypertension and the specific outcome of interests, like mortality, severe COVID-19, ARDS, Intensive Care Unit (ICU) care and disease progression were included. Electronic databases such as Pubmed, Clinical Key, Science Direct, Cochrane Library, Springer Link and Oxford Academic were used to gather studies from late 2020 to early 2022. English studies, studies related to the subject, and matching with required variables are among the inclusion criteria. Articles in the form of non-research letters, commentaries, small case series, non-English language articles and research in pediatric population (17 years of age and younger) were excluded in this systematic analysis.

2.3 Search Strategy

The systematic literature search was performed using Pubmed, Clinical Key, Science Direct, Cochrane Library, Springer Link and Oxford Academic electronic databases using the search terms: 'HYPERTENSION' AND 'CORONA' AND 'SEVERITY'. The study's publication year was limited to late 2020 to early 2022, and only published English papers were allowed. The full-texts of remaining articles were evaluated by applying the inclusion and exclusion criteria. The process of screening the title and abstract were listed in the table.

Database	Keywords	Hits
PubMed	hypertension AND corona AND severity	2678
Clinical Key	hypertension AND corona AND severity	3
Science Direct	hypertension AND corona AND severity	5
Cochrane Library	hypertension AND corona AND severity	8
Springer Link	hypertension AND corona AND severity	22
Oxford Academic	hypertension AND corona AND severity	15

2.4 Data Collection/Study Selection

To find related papers for this report, author using different databases. Keywords were used to narrow down the quest. A standardized forms containing first author, year of publication, study design, cardiovascular diseases, hypertension, need for ICU care, number of patients in severe and non-severe condition with comorbidities hypertension, and severe COVID-19 were used for data extraction. The authors look through and pick title, abstracts, and keywords from papers found through a search. We also looked through the reference lists of the papers we chose for analysis to see if any other studies were relevant. Articles that fulfill criteria were selected, screened, and analyzed. The result was summarizes using a graphic.

2.5 Quality Assessment and Data Synthesis

The quality of each included article was assessed by screening method for data extraction from the titles and abstract in the articles to identify potentially eligible studies based on the following dimensions: COVID-19 cases selection, comparability and outcomes of disease severity or fatality. The cases selection contained: the representativeness of the cases, the appropriate determination of severe cases, the appropriate determination of non-severe cases, the appropriate determination of hypertension. The key results and characteristics of each analysis are then extracted using the data extraction table.

3. Results

Through multiple database searches, most of which were excluded after screening for duplication, titles and abstracts, access to full-text articles, and suitability of the variables studied, a total 2731 studies were identified. The result from each database was

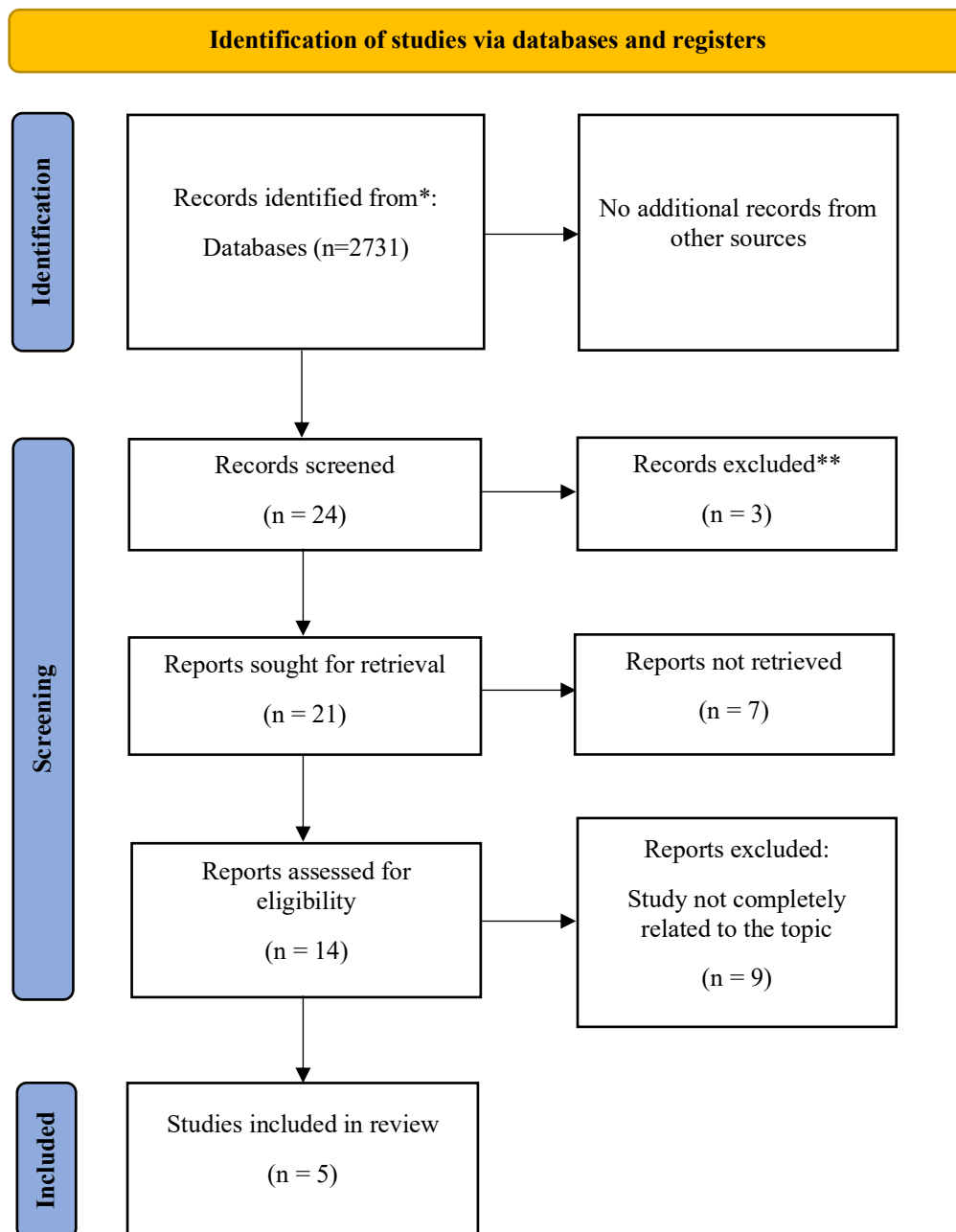
summed up in the table. After screening by title and abstract, a total of 14 studies matches the eligibility criteria. Five articles were included in the study after reading the full-text. The study was carried out in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.

3.1 Study Characteristic

The studies that were included as systematic reviews took data from late 2020 to early 2022. All studies in this review are systematic review, meta-analysis, meta-regression and multicenter retrospective cohort studies. The findings of the 5 selected studies are summarized and the characteristics of the selected studies, including their content and findings. All studies report that hypertension was associated with increased composite poor outcome that consists of mortality, and severe COVID-19.

4. Discussion

The results revealed that COVID-19 patients with hypertension were associated with a significantly increased risk of developing into the critical or mortal condition. Hypertensive patients with SARS-CoV-2 infection were shown have higher risks of severity and fatality compared to the COVID-19 cases without hypertension. In recent years, it has been well recognized that noncommunicable diseases (NCDs), including hypertension, are the main health issue, since $\pm 70\%$ of the causes of death in the world (57 million deaths/year) are attributed to NCDs. However, the sudden emergence of COVID-19, a communicable disease (CD), has changed our concept toward health and diseases.



To cope with this new disease entity, it is necessary to know the facts with regard to COVID-19 and NCDs. One potential explanation is the direct injury mediated via angiotensin-converting enzyme 2 (ACE2). Similar to SARS-CoV, a Chinese study recently indicated that SARS-CoV-2 infection was caused by binding of the viral surface spike protein to ACE2 receptor following activation of the spike protein.

ACE2 is a monocarboxy peptidase best known for cleaving several peptides within the renin-angiotensin system. Since its discovery in 2000, ACE2 has been considered as a protective factor against increases in blood pressure. Therefore, it is rational to hypothesis that the binding of SARS-COV-2 to ACE2 can reduce the physiological function of ACE2, and then lead to acute adverse outcomes of hypertension such as multi-organ dysfunction. Besides, several studies have

indicated that ACE2 played a critical role in acute lung disease, especially acute respiratory distress syndrome.²¹ This is especially true for hypertension because severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), a novel virus that causes COVID-19, utilizes angiotensin-converting enzyme (ACE)-2, one of the components of the renin-angiotensin system (RAS), for its entry into the body and because hypertension associated diseases have been revealed to be factors contributing to the severity of COVID-19.

Based on the meta-analysis study, hypertension was shown to be associated with increased composite poor outcome that consists of mortality, severe COVID-19, ARDS, need for ICU care and disease progression in patients with COVID-19. This association was influenced by gender, but not age, cardiovascular disease, diabetes and COPD. Individuals with hypertension tend to more severely affected by COVID-19, with ACE2 becomes a likely explanation.²¹ It is likely that novel coronavirus responsible for COVID-19 worked through a similar pathway as the coronavirus that caused SARS-CoV, where they use ACE2 on the surfaces of epithelial cells as a receptor to attach and enter the host pneumocytes. Activation of the renin-angiotensin system (RAS) in various tissues is associated with conditions such as hypertension. Regular use of medications, including ARB and ACEI upregulates ACE2 expression, therefore facilitating the entry of SARS-CoV-2 into pneumocytes which ultimately increases the severity and fatality of infection.

The interplay between hypertension, gender and RAS may be the explanation of our result regarding the association of hypertension and outcome in a lower percentage of male patients. In hypertensive females, there is greater activity of Angiotensin II type 2

receptor (AT2R) than angiotensin II type I (AT1R) which translates into attenuation of harmful response of AT1R activation.²² More expression and activation of AT1R are seen in hypertensive males and hypothesized in causing vasoconstriction, pro-inflammatory response, increasing oxidative stress, leading to ARDS in severe COVID-19.²³ This condition provides an explanation for the higher incidence of severe COVID-19 in males compared to females. Oestrogen is postulated in bringing the predisposition towards 'good' RAS in females. Male patients are more susceptible to develop into the critical or mortal condition than female patients, possibly because of the protection of X chromosome and sex hormones, which play an important role in innate and adaptive immunity. At the same time, men tend to be associated with bad lifestyle habits such as smoking and underlying diseases, which are reported to be associated with an increased risk of critical COVID-19.²⁴

The epidemiological data of SARS-CoV-2 infection suggested that severe COVID-19 cases were more likely to be older patients with underlying comorbidities (such as diabetes mellitus and hypertension)^{12,18,25} indicating that age was an important risk factor of severity and fatality of COVID-19. A systematic review and meta-analysis research conducted by Yanbin, Du et al shown that age had a significant effect on the association between hypertension and mortality of COVID-19 patients. Older patients (age >60 years) with hypertension had a 3.12-fold higher risk of COVID-19 death. This may be because the elderly weight and muscle mass start to decline, and cause immune senescence. In addition, older people are more prone to develop diabetes, hypertension, and cardiovascular diseases, which are reported to be associated with an increased risk of critical COVID-19.²⁴

Authors	Year	Study	Population	Outcome
Pranata, Raymond, et al	2020	Systematic review, meta-analysis, meta-regression	All research studies enrolling adult COVID-19 patients with information on hypertension and the specific outcome of interests – mortality, severe COVID-19, ARDS, intensive care unit (ICU) care and disease progression. There were 848 records after initial database searching. After screening and exclude process, the residual articles were then evaluated for eligibility by assessing its full-text article. Thereby, 30 studies with a total of 6560 patients were included in the final qualitative and quantitative synthesis.	This meta-analysis showed that hypertension was associated with increased composite poor outcome, that consists of mortality, severe COVID-19, ARDS, ICU care and disease progression. Meta-regression analysis showed that the association between hypertension and increased composite poor outcome was influenced by gender, but not by age, cardiovascular diseases, diabetes and COPD. Sub-group analysis for studies with a percentage of males $\geq 55\%$ has lower RR for composite poor outcome compared to $< 55\%$. Sub-group analysis for studies with median age ≥ 55 years old has only a slightly higher RR for composite poor outcome compared to < 55 years old.
Zhang, Jingqi et al	2020	Meta-analysis	All included studies were retrospective studies. 12 publications with 2389 COVID-19 patients (674 severe cases) were included for the analysis of disease severity and six studies with 151 deaths of 2116 COVID-19 cases were included for the analysis of disease fatality. In the present meta-analysis, relevant studies were identified by searching PubMed, Elsevier Science Direct, Web of Science, Wiley Online Library, Embase and CNKI up to 20 March 2020.	The severity rate of SARS-CoV-2 infection in hypertensive patients was much higher than in non-hypertensive cases. As severity of illness was significantly correlated to age in COVID-19 cases, it performed a subgroup analysis to evaluate the effects of hypertension on the COVID-19 severity in different age groups. As the results shown, the pooled ORs of COVID-19 severity for hypertensive patients vs. non-hypertensive cases was in age < 50 years and ≥ 50 years patients, respectively. The fatality rate of SARS-CoV-2 infection in hypertensive patients was 17.72%, which was much higher than in non-hypertensive cases (4.22%). Pooled analysis showed that hypertensive patients carried a nearly 3.48-fold higher risk of dying from COVID-19. Similarly, stratified analysis results further suggested the pooled ORs of COVID-19 mortality for hypertensive patients vs. non-hypertensive cases were in age < 50 years and ≥ 50 years patients, respectively.

Du, Yanbin, et al	2020	Meta-analysis	A total of 24 observational studies with 99,918 COVID-19 patients were included in the meta-analysis. The Medline, PubMed, Embase, and Web of Science databases were systematically searched until November 2020.	A random-effects model was applied, showed that COVID-19 patients with hypertension were associated with a significantly increased risk of developing the critical illness. In addition, pooled results based on the adjusted OR showed that hypertension is an independent risk factor for critical COVID-19. Geography, ages, and sample sizes had no significant difference in the effect of hypertension on critical COVID-19. However, male patients had a slightly higher risk of critical COVID-19 than female patients. Random effects model revealed that hypertension significantly increased COVID-19 mortality and showed that hypertension was an independent risk factor for COVID-19 mortality. Meta-regression analysis results also showed a significant influence of increasing age on the association between hypertension and mortality of COVID-19. Subgroup analyses indicated that patients with hypertension and age >60 years had a significantly higher COVID-19 mortality than age <60 years.
Zaki, Nazar, et al	2020	Systematic review	54 articles were considered for a full review. The ultimate list of 54 articles was split into six categories, with 7 articles focusing on cancer, 11 on diabetes mellitus, 7 on kidney issues, 9 on stroke, 12 on hypertension, and 8 on high cholesterol	This study shows that the risk of respiratory disease is significantly higher in patients with hypertension. Patients with hypertension were also found to be at higher risk of acute respiratory disease and chronic lower respiratory disease, independent of age, sex, smoking status, and BMI. It was observed that diabetes, hypertension, and cholesterol levels possess an apparent relation to COVID-19 severity. This study also reviewed several articles that show that hypertension is one of the major comorbidities of fatality COVID-19 cases. COVID-19 patients with hypertension have a significantly higher mortality risk. It is found that among the 1382 patients (mean age \bar{x} 51.5 years) 57.74% males, patients with hypertension had a significantly increased risk of ICU admission.

Mubarik, Sumaira, 2021 et al	Multicenter retrospective cohort	The study population was all (n = 1,833) the deceased COVID-19 patients aged 18 years or more who were admitted to the designated hospitals between December 1, 2019 and February 24, 2020, with laboratory-confirmed COVID-19 infection according to the diagnostic criteria of the new coronavirus infection pneumonia diagnosis and treatment plan (trial fifth version)	Among the 1,833 patients diagnosed with and died from the COVID-19 illness in more than 200 health facilities in Wuhan, China between December 1, and February 24, 2020, and 742 (40.5%) patients had hypertension. Of the total 1,833 patients, 1,211 (66.10%) were men, and the median age was 73 years in patients with hypertension and 72 years in patients without hypertension. After the propensity score-matching for age and sex, the median age of COVID-19 patients was 71 years in the both the hypertension and non-hypertension groups. The higher risk of mortality in patients with hypertension in reference to that in patients without hypertension was statistically significant and was almost of the same magnitude in patients with moderate, severe and critical illnesses, but was less and statistically insignificant, in case of the mild COVID-19 illness. The mortality risk estimates for the severe and critical COVID-19 illnesses in patients with hypertension were approximately double those in patients without hypertension
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The China CDC recently reported that patients aged ≥ 80 years had the highest case fatality rate, among different age groups.²⁶ This shown that hypertension was significantly associated with the severity and fatality in SARS-CoV-2 infection in both age. The current results provided further evidence that hypertension could significantly increase the risks of severity and fatality of SARS-CoV-2 infection.

This study has several limitations. Firstly, publication bias is inevitable in any meta-analysis, and some relevant articles might be missed as we only included English written studies. Secondly, we could not address the potential impact of anti-hypertension medicines although most hypertensive cases might be treated. Thus, it would underestimate the true difference in severity and fatality of SARS-CoV-2 infection between patients with and without hypertension. Thirdly, the label hypertension is not universal, the included studies may have different definition of hypertension. The stage of hypertension and whether they are controlled or poorly controlled were also unknown. Data on chronic hypertensive medications were not adequately reported by the included studies, and so cannot be analysed. Such data may provide insight on the ACEI/ARB impact on prognosis. Last, majority of the studies originated from China, the patients perhaps overlapping across the reports and some of the studies included were retrospective in design, so there may be a bias regarding collecting medical information in a retrospective manner. Therefore, caution should be considered to interpret findings.

5. Conclusion

Hypertension was associated with increased mortality, severe COVID-19, ARDS, need for ICU care and disease progression in patients with COVID-19. Hypertension is a clinically important risk factor for the adverse

outcomes of patients with COVID-19. Therefore, COVID-19 patients with hypertension should be paid more attention to in hospitals, particularly those male patients or those older than 60 years. The current results provided further evidence that hypertension could significantly increase the risks of severity and fatality of SARS-CoV-2 infection. Hypertension was associated with the increased risk of mortality in COVID-19 patients independent of the age, sex, comorbidities, and the number of underlying diseases. The magnitude of the associations of the demographic and clinical characteristics of the patients with the risk of mortality in COVID-19 illness (advanced age, male sex, COVID-19 severity, and underlying comorbidities) was higher. Therefore, it is necessary to establish awareness programs, implement effective preventive policies to improve the outcomes of SARS-CoV-2 infection in persons with hypertension, which should be helpful for the reduction in the global burden of the disease.

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