

The Association Between COVID-19 and Hypertension: A Literature Review

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Abstract

Hypertension is a highly prevalent disorder and is estimated to affect at least one in every four individuals. Developing hypertension is mostly dependant on the patient's lifestyle. It was reported among the comorbidities that were reported with the severity of COVID-19 infection. Reports showed that it is the commonest comorbidity that is associated with COVID-19 infection and severity. The prevalence of hypertension in COVID-19 patients is hugely variable and a rate of 15 - 35% has been reported by various investigations. Moreover, hypertensive patients are most prone to develop severe complications. The presence of hypertension and cardiovascular diseases were associated with increasing the risk of mortality by 2 - 3 times. Many reports estimated a significant association between hypertension and other comorbidities and mortality among COVID-19 patients. Additionally, the effect of hypertension is exaggerated when present with other co-morbidities as diabetes. Regarding the renin-angiotensin-aldosterone system (RAAS) inhibitors administration for controlling blood pressure in hypertensive COVID-19 patients, available data showed that no significant side effects were associated with these types of drugs. In fact, a previous report showed that RAAS inhibitors were significantly associated with reduced COVID-19 risks for developing severe disorders and death. Therefore, all theoretical approaches about the harmful effects of RAAS inhibitors when associated with COVID-19 infection should be ignored.

Keywords: Hypertension; COVID-19; Angiotensin; RAAS Inhibitors; Blood Pressure; Cardiovascular

Introduction

COVID-19, a novel disease caused by the SARS-CoV-2 virus, was first reported in China in December 2019 and was transmitted as a zoonotic infection from wild animals in a wet market in Wuhan [1]. In the following months, the diseases have affected almost all countries all over the world with millions of cases and deaths [2,3]. Although many coronaviruses have been linked to causing flu-like symptoms only, SARS-CoV-2 was found to cause severe respiratory distress similar to that caused by other coronaviruses including the severe acute

respiratory syndrome coronavirus (SARS), and the Middle East respiratory syndrome coronavirus (MERS) [4,5]. Moreover, these viruses had similar clinical presentations as cough, fever, dyspnea, and myalgia, however, gastrointestinal manifestations are less reported with COVID-19 disease [6].

At first, the infection was thought to cause respiratory-related symptoms only as indicated by investigations from China and Italy earlier at the beginning of the pandemic [7-9]. However, primary reports that investigated this phenomenon were then proved partially wrong as other subsequent investigations showed that COVID-19 disease has been linked with many other extra-pulmonary manifestations affecting various organs of the human body [10]. It has been indicated that COVID-19 disease, a communicable disease, has been linked with the increased incidence of many non-communicable disorders [11]. For example, kidney damage, pancreatic inflammation, neurological and cardiovascular disorders have been reportedly associated with COVID-19 [10,12-21]. This was explained by previous studies which showed that the SARS-CoV-2 causing the current pandemic has been associated with increased affinity to angiotensin-converting enzyme 2 (ACE2) receptors more than other viruses which may explain the occurrence of the extra-pulmonary symptoms [10,22].

Hypertension was reported among the comorbidities that were reported with the severity of COVID-19 infection [18,20,21,23,24]. The global prevalence of hypertension has been estimated to be 25% approximately [25]. A previous report estimated that hypertension will affect 1.5 billion people globally with an estimated prevalence rate of 60% [26]. The incidence of hypertension has been associated with many factors, most of which are related to the patients' demographics and lifestyle [27]. Therefore, to avoid the development of hypertension and its complications, blood pressure control should be approached. Recently, since the pandemic started, data of previous research linked between hypertension and COVID-19 infection and severity [18,20,21,23,24]. Many aspects have been previously investigated. In this study, we aim to review the association between hypertension and COVID-19 infection in terms of prevalence and effect on disease morbidity and the effect of antihypertensive drugs and their association with COVID-19 infection.

Methods

We performed an extensive literature search of the Medline, Cochrane, and EMBASE databases on 24th October 2020 using the terms (coronavirus disease 2019 OR COVID-19 OR severe acute respiratory syndrome coronavirus-2 OR SARS-CoV-2) AND (hypertension OR high blood pressure). Papers discussing the association between hypertension and COVID-19 infection were screened for relevant information. There were no limits on date, language, age of participants or publication type.

Results and Discussion

Hypertension effect on COVID-19 infection and prognosis

The prevalence of hypertension among COVID-19 patients

Early reports from China indicate that chronic co-morbidities as diabetes, cardiovascular disorders, and hypertension were associated with COVID-19 infected patients [15,16,18,20,21,23,28-30]. The prevalence of hypertension among COVID-19 patients was reported by a variety of investigations and has been estimated to be 15 - 35% [15-19,21,23,24,31]. However, many variations were noticed among these studies which are probably due to the difference in the included patients' demographics, like old age which is considered as a risk factor for many comorbidities and chronic disorders like hypertension, between them. Moreover, the presence of hypertension and cardiovascular diseases were associated with increasing the risk of mortality by 2 - 3 times [28]. A previous meta-analysis conducted by Li, *et al.* [28] analyzed the data from 6 original investigations and found that hypertension was prevalent in 17.1% COVID-19 patients while cardiovascular diseases and diabetes were prevalent in 16.4%, and 9.7%, respectively, among the same population. Another meta-analysis by Yang, *et al.* [30] that analyzed the outcomes of 46,248 COVID-19 patients reported that hypertension was one of the most prevalent disorders in these patients. Similarly, Emami *et al.* [32] conducted a meta-analysis of 76,993 COVID-19 patients to find the factors associ-

ated with hospitalized COVID-19 patients. The authors reported that hypertension was the most prevalent disorder with a prevalence rate of 16.37% followed by other cardiovascular, smoking, and diabetes. However, a significant heterogeneity was found between the analyzed studies due to different study designs, although previous similar meta-analysis showed similar findings.

Effect of hypertension on the severity of COVID-19 infection

The effect of hypertension on the severity of COVID-19 disease can be achieved by comparing the outcomes of patients with mild and severe outcomes that had co-existing hypertension before the infection. First reports from China indicated that hypertension and other comorbidities were significantly associated with severe COVID-19 infection in terms of intensive care unit (ICU) administration, being on mechanical ventilation, and mortality [21,23,24,28,33,34]. However, these outcomes were questioned as the authors did not study the significance of patients' demographics and clinical picture and the co-existence of other comorbidities with hypertension. Chen, *et al.* [23] also performed a descriptive study of 113 COVID-19 dead patients to study which factors were significantly correlated with the severity and death from the disease. The authors reported that hypertension, among other comorbidities, was significantly associated with the reported mortality. However, a significant difference was also estimated in terms of age, and sex between the dead and survivors of this study. In other terms, Shi, *et al.* [18] reported that the presence of hypertension and other comorbidities in COVID-19 patients was significantly associated with a myocardial injury which was in turn associated with higher mortality rates. However, the authors did not investigate which comorbidity had the most significant effect on the myocardium, and old age was significantly associated with the incidence of injury. In the same context, Zhou, *et al.* [21] conducted a cohort study to investigate the factors that can be used as predictors for COVID-19 mortality. The authors reported that hypertension was one of the significant factors that were associated with COVID-19 mortality, however, as with the case of the aforementioned studies, after adjustment of the patients' demographics, hypertension, and other comorbidities were no longer significant factors. Similar results were reported by Guo, *et al.* [16] where old age, being male, and renal dysfunction and administration of RAAS blockers were also associated risk factors for an increased incidence of myocardial injury. However, it is worth mentioning that the authors did not clearly define the involved cardiovascular disorders and whether hypertension was involved or not. On the other hand, Guan, *et al.* [15] studied this correlation on 1590 COVID-19 patients and adjusted the effect of age and smoking, and found that hypertension among other comorbidities was significantly associated with severe COVID-19 infection with an increased risk of 1.57-fold for hypertension. Additionally, the effect of hypertension is exaggerated when present with other co-morbidities as reported by Wu, *et al.* [29] where the co-existence of hypertension and diabetes were significant risk factors for developing respiratory distress, however no association was found regarding patients' mortalities. On the other hand, other reports did not consider hypertension as an independent risk factor the severity of COVID-19 infection [21,29,35-37]. Although hypertension was found to be significantly associated with the severity by univariate analysis, multivariate analysis showed that no significant association was found between hypertension and COVID-19 severity [21,29,35-37]. The meta-analysis conducted by Zhang *et al.* [20], however, showed that, based on the analysis of 12 studies involving 2389 COVID-19 patients, hypertension was significantly more associated with severe COVID-19 outcomes than patients with no hypertension, irrespective of the age and with no considerable heterogeneity between the included studies.

COVID-19 infection in association with RAAS inhibitors and blood pressure

The effect of ACE2 is essential in the control of hypertension as it is responsible for the activation of the renin-angiotensin-aldosterone system (RAAS) which is responsible for many mechanisms as vasoconstriction, and salt and water retention that are mainly responsible for controlling blood pressure [38]. This is achieved by the end products of the RAAS system, angiotensin II, and aldosterone. Angiotensin II is a potent vasoconstrictor that induces many harmful events as atherosclerosis, fibrosis, tissue inflammation, and myocardial hypertrophy that acts by binding to angiotensin II receptor type 1 (AT 1) [39]. As it is widely known, now, the SARS-CoV-2 virus initiates its pathogenesis by binding to ACE2 receptors in the different parts of the body [40-43]. This will consequently lead to the downregulation of the receptor and a reduced action of ACE2 in the infected organs due to severe tissue inflammation [40,44,45]. Therefore, decreased action of ACE2 will lead to increased levels of angiotensin II, but increased virulence of SARS-CoV-2 and worsening the morbidity of the

disease [46,47]. Accordingly, controversial findings have been reported by previous investigations about the role of RAAS inhibitors, including ACE inhibitors and angiotensin II receptor blockers (ARBs), in COVID-19 patients [48].

The effect of COVID-19 infection on hypertensive patients has been investigated by some studies. Ran., *et al.* [49] conducted a retrospective cohort study of 803 patients and found that 8.3% of these patients were admitted to the ICU, 3.7% had respiratory failure, 3.2% had heart failure, and 4.8% died. The authors also reported that average systolic blood pressure and pulse pressure were the only predictor factors for heart failure. Moreover, they concluded that poor blood pressure control was associated with an increased risk of developing severe COVID-19 complications. Mancina *et al.* [50] studied the correlation between COVID-19 infection and severity and the prior use of RAAS inhibitors between cases and controls. The authors reported that no association was found between previous RAAS inhibitors intake and COVID-19 infection or severity.

RAAS inhibitors are widely used in the management of hypertension, and therefore, their action on COVID-19 patients with hypertension should be investigated for any potential development of other disorders that may increase the severity of the disease. Zhang., *et al.* [51] compared the effect of whether using RAAS inhibitors or not was associated with an increased risk of severe COVID-19 disease and mortality in a Chinese population. The authors reported that RAAS inhibitors administration in hypertensive patients was associated with reduced mortality and severe adverse events among these patients. Similarly, Fosbol., *et al.* [52] reported similar results in a 4480 population-based comparative study. These results are consistent with many reports from all over the world which showed that using RAAS inhibitors effectively controls the blood pressure without causing any concerning side effects, but even enhancing patients' outcomes as reported by Zhang., *et al.* [51]. Although previous studies reported that using RAAS inhibitors was associated with an increased incidence of severe COVID-19 disorders, it has been concluded that these results are not conclusive by many studies where no association was found, and therefore these drugs were still used for the management of hypertension and cardiovascular diseases in COVID-19 patients. Therefore, claims about the hazards of using RAAS inhibitors remain theoretical, and therefore, RAAS inhibitors should be continued for treating hypertensive patients with COVID-19 infection. Moreover, no regimen switch to other modalities rather than RAAS inhibitors should be approached which can affect the blood pressure control in these patients [53].

Conclusion

Hypertension has been reported to be the commonest comorbidity that is associated with COVID-19 infection and severity. Although many investigations have been published in this field, there is still so much that we do not know about the epidemiology of high blood pressure in COVID-19 patients. The prevalence of hypertension in COVID-19 patients is hugely variable and affects almost a quarter of these patients. Moreover, hypertensive patients are most prone to develop severe complications. Regarding RAAS inhibitors administration for controlling blood pressure in hypertensive COVID-19 patients, available data showed that no significant side effects were associated with these types of drugs. Therefore, all theoretical approaches about the harmful effects of RAAS inhibitors when associated with COVID-19 infection should be ignored.

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